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ARCHIVES OF SURGERY

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ISOLATED GIANT CELL XANTHOMATIC TUMORS OF THE FINGERS AND HAND*

MICHAEL L. MASON, M.D.
CHICAGO
AND
W. H. WOOLSTON, M.D.
ALBUQUERQUE, N. M.

The isolated giant cell xanthomatic tumors arising from the tendon sheaths and other soft tissue of the extremities have been of clinical and pathologic interest for many years. Despite considerable study, their true pathologic classification is still in doubt, and unfortunately they are too often diagnosed giant cell sarcoma. The clinical picture of the tumors is well established, however, and should have some bearing on the consideration of the pathology. They are characterized microscopically by the presence of two striking elements, the foreign body giant cell and the foamy cell; once seen, this combination is never forgotten. When one considers that for many years both these cells have been shown to be nonspecific and to occur in the most diverse types of lesions and that their presence denotes the fact that foreign material is present, one must look for other factors to determine the malignancy or benignancy of the tumor.

Xanthomatic tissue appears in many forms, not only as single isolated growths, but also associated with various medical conditions and as a disease of the skin, xanthoma multiplex. In many instances the latter conditions have been shown to be associated with hypercholesterinemia, and this possibility must not be ignored in considering these growths. Pinkus and Pick, in 1908 and later in 1910, showed that there was increased cholesterol in the blood in xanthoma multiplex and in other types of xanthoma, but they thought that the isolated tumors were true neoplasms and were not associated with such an increase. Several extensive discussions of the whole subject of xanthoma have appeared recently, and to these the reader is referred (Levy, 1925; Weber, 1924; Wustmann, 1925; Stewart, 1925). In his textbook, Kauffmann discusses xanthoma under three subheads: xanthoma palpebrarum, xanthoma multiplex and xanthoma en tumeurs. He recognizes the

* From the Departments of Surgery and Anatomy, Northwestern University School of Medicine, Chicago.

presence of an increased blood cholesterol in xanthoma multiplex, although he remarks that not all cases show such an increase. He does not suggest that such an increase is present in the xanthoma en tumeurs, but he does not classify this condition with tumors of the tendon sheath, though he does remark that they are greatly similar in pathology. Stewart gives a brief but excellent summary of the growths containing foamy cells, and divides them into two large groups, those with an increased blood cholesterol and those without such an increase. To the first group he adds the various dermatologic manifestations of xanthoma (xanthoma palpebrarum, xanthoma multiplex, xanthoma planum, xanthoma tuberosum and other forms), xanthomas occurring in diabetes, renal and hepatic disease, the strawberry gallbladder, the cholesteatomas of the choroid plexus and arterial atheroma. To the second group he assigns the myeloid kidney, myeloid tumors of the tendon sheaths (which he thinks are endotheliomas), retention cysts of the breast, cerebral softening, dermoid cysts, mycosis fungoides, certain thyroid lesions and such foamy cell deposits as occur in subacute and inflammatory conditions. Levy (1925) also separated the tumors of the tendon sheath from the xanthelasmas accompanied by hypercholesterinemia. Weber (1924) thought, however, that they are all associated with an increased blood cholesterol. Cases of xanthoma multiplex have been reported in which no such high cholesterol values have been found (Rosenthal and Braunisch, 1921). The evidence for hypercholesterinemia in the isolated tumors is inferential. We have not found any published results of such an increase in any of these tumors.

The first reference in the literature to the yellow tumors is by the French dermatologist, Rayer (1835), who pictured in his textbook the yellow plaques of the eyelids (xanthoma palpebrarum). Lebert (1845) noted the yellow color of these soft tissue tumors and gave the name "xanthos" to the coloring substance, which was thought at the time to be a peculiar fat. Addison and Gull (1851) described five cases of multiple xanthoma associated with liver (jaundice) and pancreatic (diabetes) disturbances. Paget, in his "Lectures on Surgical Pathology" (1853), described the pathologic picture of the yellow tumors which he notes as coming from various tissues, the breast, cerebral membranes, subcutaneous tissues and the uterus. The earliest references to the yellow giant cell tumors of the tendon sheaths are from Broca (1860) and Czerny (1869). The majority of the early references are in the French literature, in which are found two good reviews of these isolated tumors; the earlier one by Heurtaux (1891), who considered only the giant cell tumors of the tendon sheath; the other by Tourneux (1913), who collected reports of all cases of tumors of the tendon sheath, among them fifty-four reports of the giant cell type. It is probable that many

of the cases collected by Tourneux were of the xanthoma type, though they were not so recognized at the time (Garrett, 1924).

At the suggestion of Dr. A. B. Kanavel, we took up the study of these tumors and have eight cases to report, four of them from the service of Dr. Kanavel at Wesley Memorial Hospital, Chicago; one from Dr. H. M. Richter; one from Dr. J. R. Buchbinder; one from the late Dr. William Schroeder, and one from Dr. W. H. Woolston, who began the study of these tumors on the service of Dr. Kanavel and who collaborated in the study.

REPORT OF CASES

CASE 1.—Mrs. D., aged 54, a housewife, was operated on in March, 1919, for a small tumor of the size and shape of a bean on the distal phalanx of the left little finger. The tumor was smooth, firm and freely movable under the skin. It had appeared four years previously and was caused, she thought, by irritation

Fig. 1.—The tumor in case 3 (Mr. R.). It lay on the ulnar side of the right index finger, was smooth, lobulated and had the consistency of a fibroma. It was not connected with the tendon sheath.

from a ring on the finger next to it. Three years before the operation she had caught the tumor between two boxes, and this trauma had stimulated its growth. During the year before operation it had grown more rapidly. At operation a yellowish encapsulated tumor was found. It lay in the subcutaneous tissues and did not show any connection with tendon sheaths, joint or bone. Microscopically, it was a characteristic xanthoma (figs. 9 *B* and 14 *C*). There were large areas of xanthoma cells (fig. 9 *B, F.C.*) and numerous giant cells of the foreign body type. Many small blood vessels were seen, such as one might expect to see in chronic inflammatory tissue (fig. 14 *C*); blood sinuses were present but not abundant, and hemosiderin was seen in moderate amount. Some small isolated groups of xanthoma cells were noted. There was some suggestion of an alveolar formation in the tumor. The tumor has not recurred to date after a complete local removal.

CASE 2.—Mrs. Wa., aged 53, a housewife, was operated on in September, 1920, eighteen months after the second phalanx of the right middle finger was crushed in a washing machine. A small tumor about the size of a cherry had developed at this place without pain, slowly and steadily, causing her no trouble

except the thought that it might be malignant. At the time of operation an encapsulated tumor was found attached to the tissues over the first and second phalanges, but apparently not to the tendon sheaths. A frozen section was made at the time of operation, and the diagnosis returned was giant cell sarcoma. After this the finger was amputated along with the head of the third metacarpal bone. The microscopic section (figs. 5 *C* and 11 *A*) revealed a tumor a great deal like that in case 1, polymorphic in its cells and in its make-up. Some areas were trabeculated (fig. 5 *C*), and many endothelial cells and fibroblasts were seen, often filled with pigment. Recent hemorrhages suggested the origin of the pigment, which gave a Berlin Blue reaction for iron. Giant cells were numerous, but the xanthoma cells were not so frequent as in case 1. Blood vessels were not plentiful and tended toward the adult type. There has been no recurrence to date.

Fig. 2.—The tumor in case 6 (Mother A.). It lay on both volar and dorsal surfaces of the right wrist and had involved tendon sheaths, joint capsule and bone. It was removed in two stages. Previous to the first operation it was thought to be tuberculous.

CASE 3.—R., between 50 and 60 years of age, a tradesman, was operated on in February, 1921, ten months after a smooth lobulated tumor (fig. 1) had appeared on the right index finger, following injury with a bowling ball. In the interval before operation the tumor had grown to the size of a walnut. It caused no pain or functional disturbance. The tumor was freely movable under the skin and did not move with the tendons. At operation it was found to be well encapsulated and to be attached to the fibrous tissue on the ulnar side of the finger, and it did not involve the tendons or tendon sheaths. It was smooth and lobulated, and on cut section had the peculiar yellow areas so characteristic

of the xanthomas. There was no infiltration of the bone. On microscopic examination (figs. 6 *A*, 10 *B* and *C* and 11 *B* and *C*) the picture was polymorphic; a connective tissue capsule sent down into the tumor numerous trabeculae (fig. 6 *A*), which divided it into alveoli containing various sorts of cells. The trabeculae were not present throughout the tumor, but in the deeper parts were replaced by an amorphous material which contained fewer cells. The giant cells (figs. 6 *A* and 11 *B* and *C*) were of all types, sizes and shapes and contained as many as a hundred or more nuclei; some foamy giant cells, such as Spiess described, were seen (fig. 11 *C*). Foamy cells were liberally scattered throughout the tumor, both as small isolated groups and as large areas. Cholesterol clefts (fig. 10 *C*, *C.C.*) were seen in the central parts of the tumor. We were not able to get an unfixed section of the tumor to see whether it contained crystals of

Fig. 3.—The hand in case 7 (Mrs. G.). The tumor lay on the ulnar side of the right middle finger. The skin was not involved, and no connection with the tendon sheath was made out. Microscopically it was a typical xanthoma.

cholesterol, although this observation has been confirmed numerous times. Blood vessels were numerous and of the adult type. Fibroblasts and endothelial cells were frequent. Some pigment was present, but no recent hemorrhages were noted. No round cell or polymorphic infiltration was seen. The tumor has not recurred since its removal six years ago.

Case 4.—Mrs. We., a housewife, aged 55, presented a small, lobulated, rather firm tumor which had been slowly growing on the dorsum of a finger for several years, but had not caused pain or functional disturbance. At the importunities of

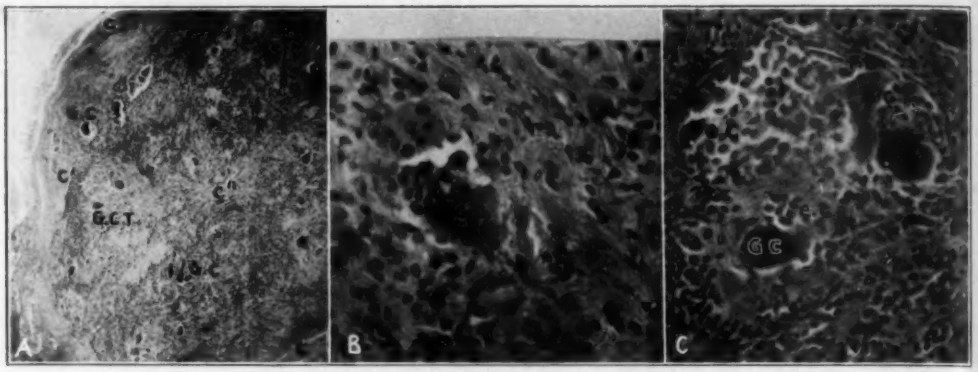


Fig. 4.—Photomicrographs of sections through the tumors. *A* (case 4). A distinctly encapsulated tumor which contained no xanthoma cells, but a great number of giant cells. The capsule, *C*, is shown surrounding the tumor and sending into it strands of connective tissue which tend to lobulate it, *C'*. Bands of connective tissue and fibroblasts ran throughout the tumor, *C''*. Many giant cells, *G.C.* and *G.C.T.*, were seen, giving the appearance of a giant cell tumor of the bone. *B* (case 8). Two giant cells, *G.C.*, lying in a connective tissue and fibroblastic group of cells. The alveolar formation was noted here. *C* (case 4). The group of giant cells, *G.C.*, under high magnification showing three large giant cells, *G. C.*, and numerous other small ones lying in an alveolus, with other types of cells, probably endothelial, *E.C.*, and *F.B.*, fibroblasts.

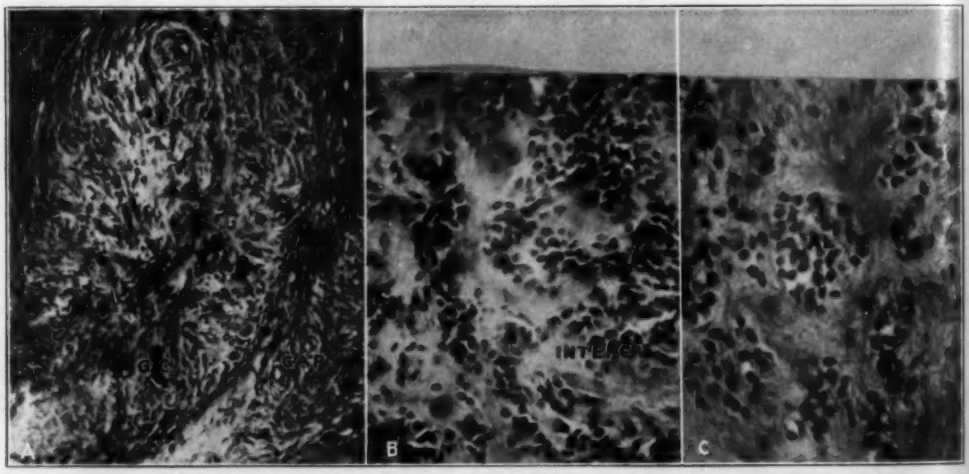


Fig. 5.—*A* (case 7). An area from the tumor made up of confusing whorls of spindle cells and connective tissue, that might easily be taken for a fibroma. A few giant cells, *G.C.*, and some small capillaries, *CAP.*, were seen. *B* (case 4). This shows the amorphous intercellular substance, eosinophilic, *INTERC.*, which contained a few nuclei. The other cells were fibroblastic and endothelial. *C* (case 2). A somewhat similar area in another tumor. An alveolus, *AL.*, was noted, containing what appeared to be endothelial cells.

a nephew, a physician, she had it removed in October, 1921. It seemed to be attached to the synovial membrane of an interphalangeal joint. Microscopic section (figs. 4 *A* and *C* and 5 *B*) showed that a thick connective tissue capsule (fig. 4 *A*) sent trabeculae down into the tumor, dividing it into many similar lobules. In many instances these trabeculae were fibroblastic (fig. 5 *B*). Endothelial cells (fig. 5 *B*) and giant cells (fig. 4 *C*) were frequent. Areas of pigment were seen at the periphery of the tumor, but no area of hemorrhage were noted. Xanthoma cells were not seen; since but one section of the tumor was available for our examination, we cannot say that foamy cells were absent, as we have noted that they are often absent from parts of a tumor, while they are numerous in other parts. The tumor has not recurred to date.

CASE 5.—S., a dentist, aged 31, was operated on in July, 1924, about a year after a small tumor had appeared on the palm of the right hand, at the place where his extraction forceps rested. It was firm, lobulated and not fluctuant, and was apparently attached to the palmar fascia. It was somewhat tender. For a while it had grown slowly and without pain, but recently it had taken on more

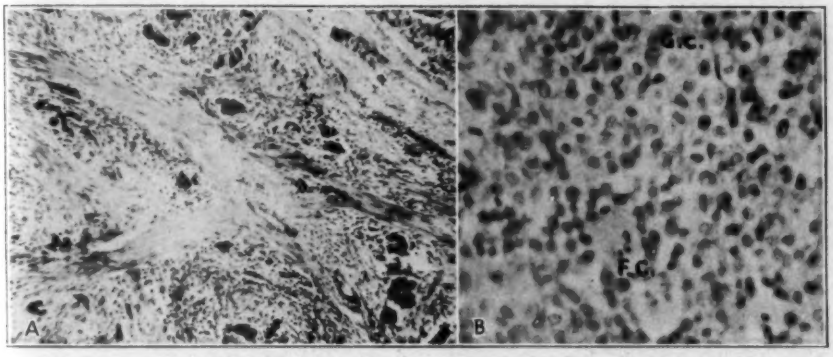


Fig. 6.—*A* (case 3). In this section the strands dividing the tumor into alveolae were more adult in type; numerous giant cells were seen in the alveolae. *B* (case 6). An endothelial cell group from the tumor. The large nucleus and the vesicular body are well shown. A foamy cell, *F.C.*, and a giant cell, *G.C.*, are also shown.

rapid growth and had attained the size of a hazelnut. At operation the yellowish growth was seen to be attached to the palmar fascia; the tendon sheaths were normal. Microscopically it was a typical xanthoma, with xanthoma cells, giant cells, fibroblasts, endothelial cells and some deposition of pigment. The growth has not recurred to date, The results of three cholesterol determinations made on the blood of this patient are shown in table 1. No increase of the blood cholesterol was found (the cholesterol determinations were made in 1927; the tumor was removed in 1924).

CASE 6.—Mother A., a nurse, aged 53, had developed a slow growing tumor on both the volar and the dorsal surfaces following a fall on the right wrist nine years previous to admission. It had been associated with pain ever since its onset. Operation was first performed in February, 1926. During the previous year the tumor had grown more rapidly, the pain had been more severe, and some tingling of the fingers was present. On examination, the resemblance to tuberculous

tenosynovitis was striking, and the growth was diagnosed as such before operation. It was large, nodular and soft, was over both the volar and dorsal surfaces of the wrist and, from external examination, seemed to involve the tendon sheaths. The skin was freely movable over it. The volar mass was the first to be removed in February, 1926 (fig. 2). The volar mass was composed of yellowish, granulation-like tissue involving the tendon sheaths but not the tendons. It lay under the volar carpal ligament and on the pronator quadratus and had involved the metacarpocarpal joint of the thumb. The radius was also somewhat involved. Microscopically (figs. 6 *B*, 7 *A* and *B*, 8 *A*, 9 *A*, 10 *A*, 12 *A*, *B* and *C*, 15 *A* and *B* and 16 *A* and *B*) the mass was cellular, there was no demonstrable capsule and numerous endothelial cells and fibroblasts were seen. The blood vessels were of the adult type in many instances, but in places were seen those changes described by Bellamy that led him to think that the vascular endothelium was proliferating to produce the tumor. These changes are shown in figure 12 *A*, *B* and *C*. Sinuses

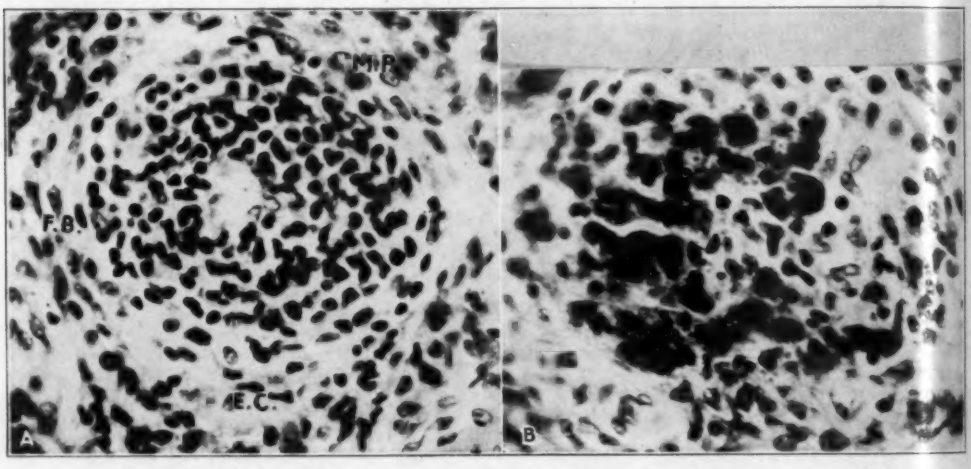


Fig. 7.—*A* (case 6). A small vessel with marked perivascular round cell infiltration. Farther out were fibroblasts, *F.B.*, endothelial cells, *E.C.*, and large mononuclear phagocytes, *M.P.* *B* (case 6). An area of deposition of pigment; the granules, which gave a positive Berlin blue reaction, were both intracellular and extracellular.

were present in this part of the tumor, but were not so prominent as they were in the second part removed. Vacuolated endothelial cells were noted throughout the tumor (fig. 6 *B*). Large phagocytic cells, at times full of pigment, were noted in all parts of the tumor. The pigmented areas seemed to be somewhat circumscribed and appeared to have resulted from small areas of hemorrhage into the tissues (fig. 7 *B*). Fresh areas of hemorrhage were noted. Foamy cells (figs. 8 *A*, 9 *A* and 10 *A*) were frequent, both as large groups and as small isolated accumulations. They appeared to develop from endothelial cells by a process of gradual vacuolization. Giant cells were scarce (figs. 6 *B*) and small, having but few nuclei; some of the cells contained pigment. A striking characteristic of this tumor, not noted in the second part removed seven months later, was the great number of eosinophils throughout the mass. They seemed to have infiltrated

the whole tumor and did not lie in masses or groups or with any perivascular arrangement. They were not noted in any other tumors seen by us.

The dorsal parts of the tumor were removed Sept. 23, 1926. At this time it was noted that the tumor had not grown and that the volar wound had healed well. The pain and tingling had practically disappeared in the interval, and no trouble had been experienced in the hand, except at one time when after a hard day's work, the hand had swollen causing pain; the swelling soon went down

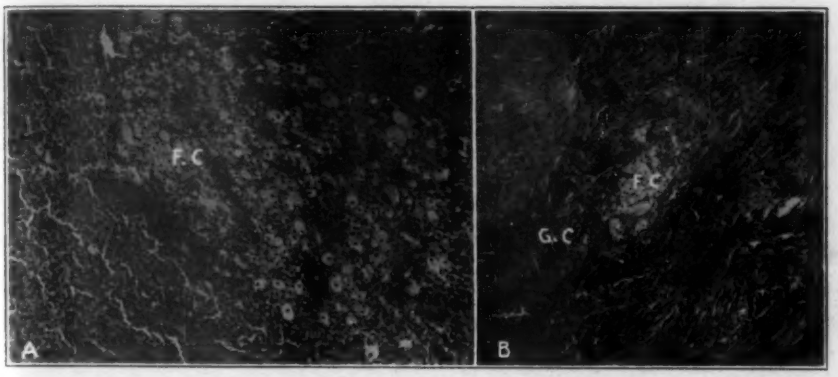


Fig. 8.—*A* (case 6). A mass of foamy cells, *F.C.*, was seen lying in an area of endothelial cells. Many were isolated, others lay in larger groups. They gave the appearance of degenerative changes *B* (case 8). A smaller mass of foamy cells, *F.C.*, lying in a fibroblastic area. A giant cell, *G.C.*, is shown here. The foamy cells appeared to be a degeneration, and suggested that a later stage will be the formation of cholesterol clefts as shown in figure 10.

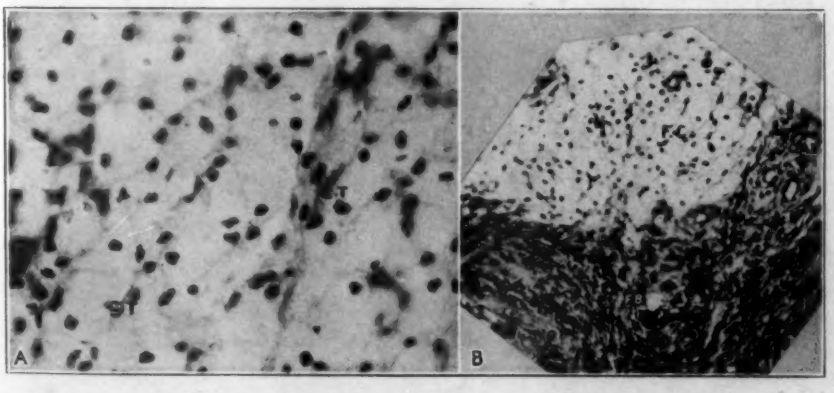


Fig. 9.—*A* (case 6). An area of foamy or xanthoma cells showing the eccentric arrangement of their nuclei and their pyknotic character. The granular and vesicular character of the cytoplasm is also well shown. Connective tissue cells, *C.T.*, formed a supporting structure for the cells. *B* (case 1). An area of foamy cells, *F.C.*, was seen lying against a connective tissue and fibroblastic area, *F.B.* Many newly formed small capillaries, *CAP.*, were seen in the connective tissue area.

however, and there was no further trouble. The mass on the dorsum was nodular and smooth and not attached to the skin. The movements of the tendons could not be felt through the tumor, and the tumor did not move with the tendons. The urine and blood count were normal, and the blood sugar was 0.09 per cent. Two determinations of the blood cholesterol were made, using the method of Bloor, with a cholesterol standard. At one time a value of 165 mg., and at another a value of 143 mg., per hundred cubic centimeters of whole blood were obtained. The roentgen ray showed some involvement of the carpal bones.

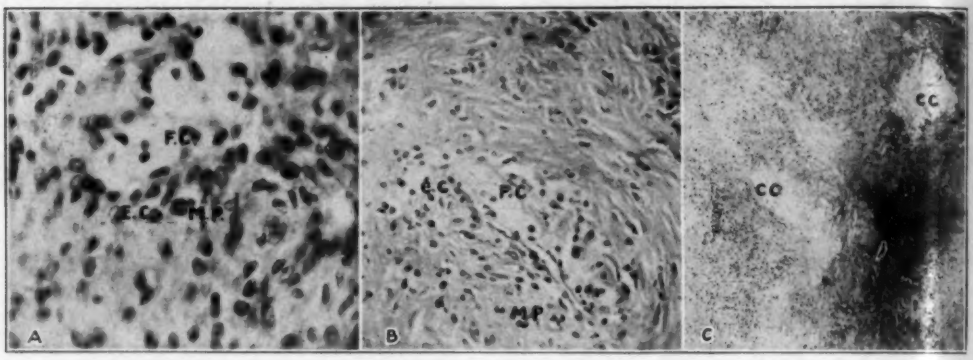


Fig. 10.—*A* (case 6). A small isolated group of foamy cells, *F.C.*, lying in the midst of an endothelial cell group, *E.C.* Some large mononuclear phagocytes, *M.P.*, were noted. *B* (case 3). Another small isolated group of foamy cells, *F.C.*, in a rather hyalinized area; some endothelial cells, *E.C.*, and large mononuclear phagocytes, *M.P.*, were also seen. *C* (case 3). Cholesterol clefts, *C.C.*, in rather dense scarlike tissue.

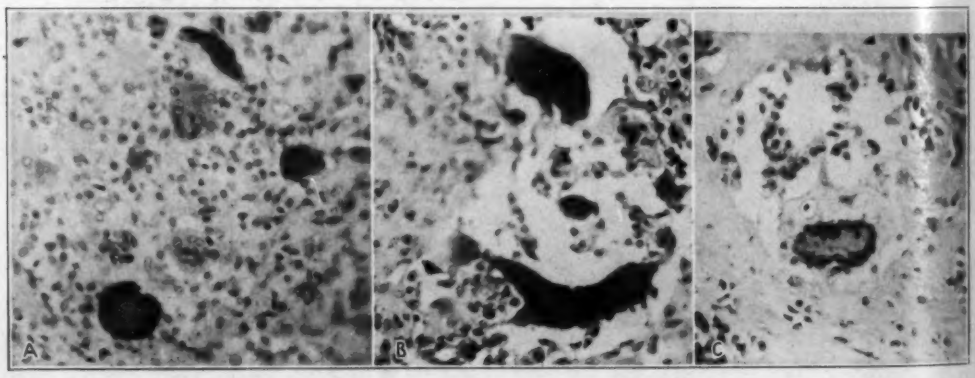


Fig. 11.—Various giant cells from the tumors (figs. 4 and 6 show others). *A* (case 2). Some of these giant cells were darkly stained and had dark elongated nuclei; others were lightly stained, and the nuclei were oval and showed a definite nucleolus. *B* (case 3). Here the giant cells had attained enormous size and lay in a clear space, probably an artefact. *C* (case 3). A large foamy giant cell such as Spiess described, the body of the cell filled with cholesterol vacuoles and other foreign detritus.

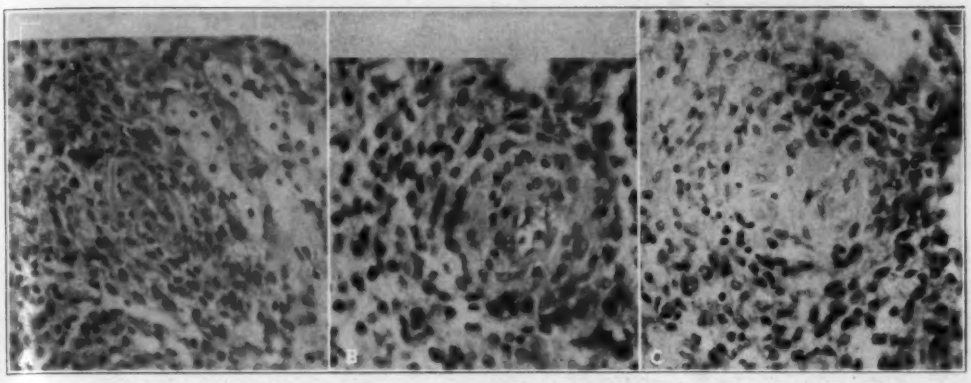


Fig. 12.—*A, B* and *C* (case 6). These photomicrographs show some constantly recurring figures, present in most of our tumors. The endothelium of the capillaries, as in *A*, was thick and swollen and was taken to indicate proliferative changes, which could be borne out in *B* and *C*. Similar capillary figures are seen, however, in inflammatory tissue. The surrounding cells are endothelial cells, large mononuclear phagocytes and foamy cells.

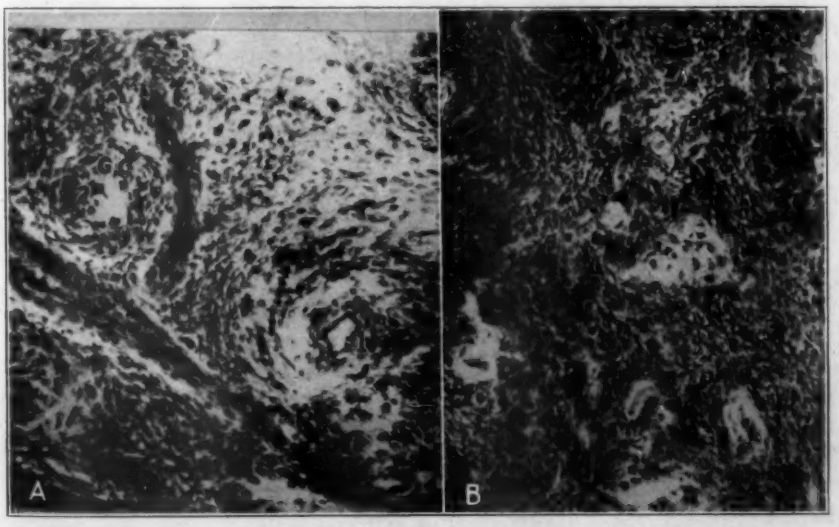


Fig. 13.—*A* and *B* (case 7). Other types of vascular changes noted. In *A* the vessel 1 had a rosette-like lining with endothelial cells, which were fat and large. In vessel 2 the proliferative changes, if such they were, had further progressed, and a giant cell, *G.C.*, was seen. In *B* is shown a rather large area in which there appeared to be numerous areas similar to *A* 2 and to figure 12 *C*.

At operation the tumor was found to involve not only the tendon sheaths, but the joint capsule of the carpus as well. The dorsal tendons were surrounded, but not involved; their tendon sheaths had been replaced by the tumor tissue. As at the previous operation, the tumor was a mixture of yellow and dark red, in spots not unlike a giant cell tumor of the bone. The carpal bones were honey-combed and were curetted out. The triquetrum was removed.

Microscopically the tissue from the joint and tendon sheaths were much alike, except that xanthoma cells were rare in the tumor of the joint. The tumor was a great deal like the volar tumor removed seven months before, the sinuses (fig. 15 *A* and *B*) had become more prominent, and the eosinophilic infiltration had disappeared. The bone removed had been invaded, and a few tumor cells were seen in its medullary cavity (fig. 16 *A* and *B*). The osteoclastic activity of the tumor was not marked, and there was no evidence of osteoplasis; the impression gained was that the invasion was one of pressure rather than true neoplastic invasion. Few giant cells were seen in any part of the tumor, and not many were seen about the invaded bone.

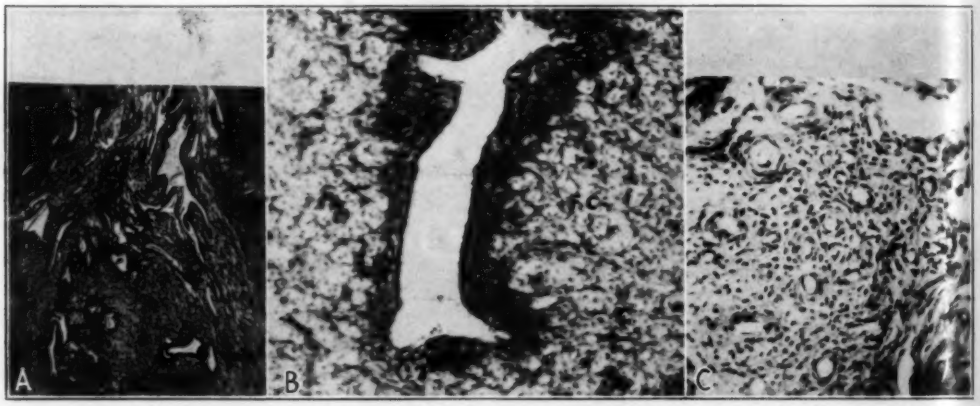


Fig. 14.—*A* (case 7). A xanthomatic area which contains numerous endothelial lined sinuses, giving the appearance of an angioma. These sinuses lay among xanthoma cells, and it appeared to us that the endothelial cells were gradually taking up cholesterol with the eventual production of xanthoma cells. *B* (case 7). A sinus under larger magnification; *F.C.*, foamy cells. *C* (case 1). A group of small capillaries such as one might expect in granulation tissue.

Case 7.—Mrs. G., aged 42, was operated on in May, 1926, for a tumor on the ulnar side of the middle finger of the right hand (fig. 3). The tumor had been present for two years, having arisen from an unknown cause. It had shown slow but steady growth from its onset, but had caused no pain or discomfort and had given her trouble only when drawing on her gloves and from the fear that it might be malignant. On examination two nodular masses were felt under the skin on the volar and dorsal surfaces of the finger; they were somewhat elongated, and the one on the flexor surface was the larger. They were freely movable under the skin, but seemed to be attached in the depths. At operation they presented the peculiar reddish and yellow coloration typical of the xanthoma, with the yellow predominating. The volar tumor was attached to the fibrous tissue about the first interphalangeal joint. The lateral digital nerve ran through it in

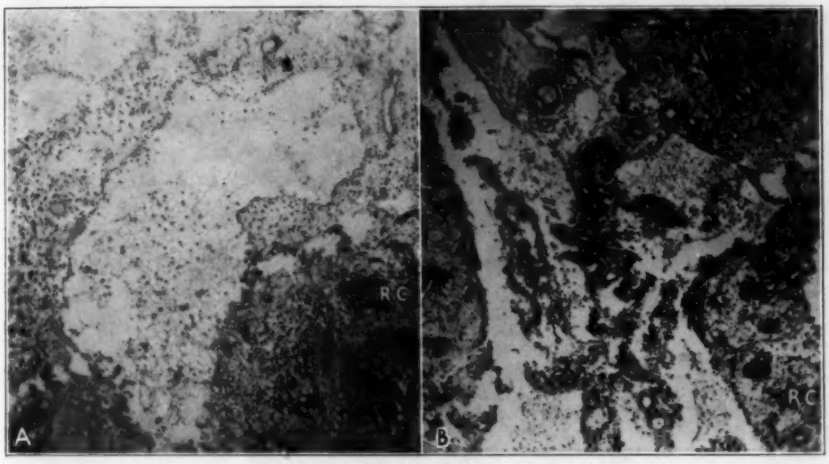


Fig. 15.—*A* and *B* (case 6), showing large sinus-like areas, somewhat similar to those in figure 14, here filled with a coagulum and many white cells. The tumor was vascular, and areas of round cell infiltration were frequent, *RC*.

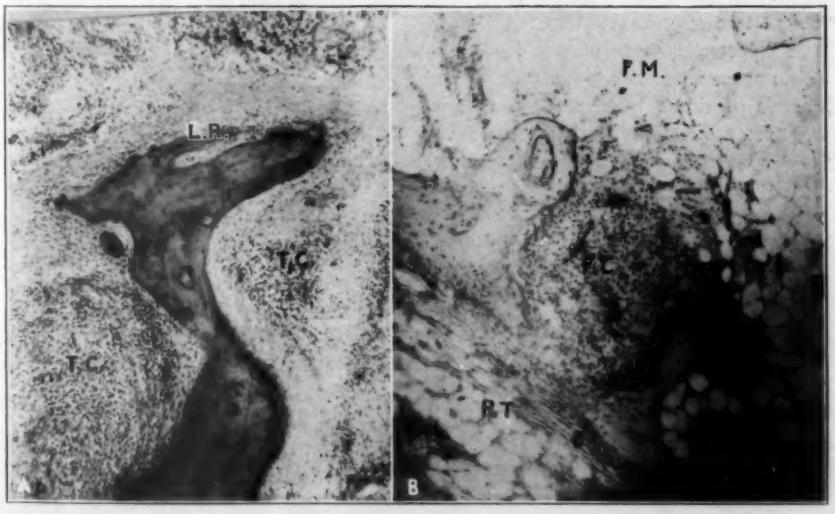


Fig. 16.—(Case 6). In *A* is shown a place on the cortex of the triquetrum through which the tumor invaded the bone. Lacunar resorption, *L.R.*, was noted, and the bone was irregular. Tumor cells, *T.C.*, were noted on both sides of the bone. Giant cells were scarce. In *B* a small group of foamy cells, *F.C.*, is seen lying in the normal fat marrow, *F.M.* A defect of the cortex is seen. The tissues about the bone, *P.T.*, were not invaded by tumor cells.

a groove on the surface. The tendon sheath was not involved. The tumor on the dorsum was rather firmly attached to the fibrous tissues about the dorsal tendons. Microscopic section (figs. 5 *A*, 13 *A* and *B* and 14 *A* and *B*) revealed a typical xanthoma. A fibrous capsule of adult connective tissue sent down strands of fibrous tissue into the tumor, which disappeared as the deeper parts of the tumor were reached. Xanthoma cells (fig. 14 *A* and *B*) were abundant in some sections, not so abundant in others. Endothelial cells were frequent and could be seen to give rise to foamy cells. Blood vessels were numerous and showed proliferative changes (fig. 13 *A* and *B*). In the foamy cell areas sinuses were present, some of which were empty; others were filled with blood and some with débris. Pigment, positive for iron, was plentiful, both intracellular and extracellular. No recent hemorrhages were seen.

A blood cholesterol determination made on this patient gave a value of 185.3 mg. per hundred cubic centimeters of whole blood. The tumor has not recurred to date.

CASE 8.—Mrs. C. G., aged 26, a housewife, operated on in February, 1927, had noted a small growth on the right thumb about a year before. She disclaimed any knowledge of a causative factor. Since the onset the growth had slowly enlarged, but it had never given her any real pain or other trouble. She said that it seemed to be tender at times, and that pressure on it nauseated her. The movements of the thumb were not interfered with. The swelling had never opened and discharged. No other similar swelling was present.

Physical examination showed a small, grape-sized, firm mass on the dorsolateral aspect of the right thumb, movable under the skin and not attached to the underlying tissues. It was diagnosed as a benign connective tissue tumor.

At operation an irregular, lobulated, almond-shaped tumor was removed, which looked like suprarenal tissue.

Microscopic section (fig. 4 *B*) showed the elements of a typical xanthoma. A connective tissue capsule covered one side of the tumor and sent down into it strands of tissue which gave it a lobulated appearance. Over this capsule there was some loose connective tissue in which areas of hemorrhage were seen. Xanthoma cells were rather numerous and lay in irregular groups. Endothelial cells were present and showed the gradual vacuolization with the final production of the foamy cells. Many foreign body giant cells were present. Blood vessels were not especially numerous; in spots one could see round cell infiltration about them. Pigment and sinuses were not noted.

COMMENT

Table 1 gives in summary the information concerning our eight cases. It is seen that two patients were men and six were women; with two exceptions, all were in the fourth and fifth decades of life. The right hand is most frequently affected. One tumor occurred on the wrist and the rest on the fingers. The duration varied from ten months in case 3 to nine years in case 6. Trauma seems to play a rather important rôle in our series—in three cases, severe trauma; in two, recurrent trauma. Pathologically, all the tumors contained giant cells, some in great abundance, others in smaller numbers. Xanthoma cells were present in all but one. Cholesterol determinations were made in three cases; in none of them was there an increase in the blood cholesterol. There have been no recurrences to date in any case; however, in

case 8 the interval since operation is too short to be significant. The average time since operation for the others is four and one-third years. The treatment instituted was local excision in all but one case. In case 2 the finger was amputated after a frozen section showed the condition to be giant-cell sarcoma. The tumors were all of moderate size, varying from that of a hazelnut to that of an almond, except the one in case 6, which was large and was diagnosed as tuberculous tenosynovitis.

TABLE 1.—*Data of Eight Cases Reported* *

Patient	Age	Location	Duration	Trauma	Pathology	
					X.c.	G.c.
1. Mrs. D. ..... February, 1919	54	Left fifth finger	4 years	+ (ring on adjacent finger)	+	+
2. Mrs. Wa. ..... September, 1920	53	Right third finger	1½ years	+ (crushed in washing machine)	+	+
3. Mr. R. ..... February, 1921	50-60	Right second finger	10 months	+ (bowling ball)	+	+
4. Mrs. We. ..... October, 1921	50-60	Finger	7 years	0	0	+
5. Dr. S. ..... July, 1924	31	Right palm	1 year	+ (pressure extraction forceps)	+	+
6. M. A. ..... February, September, 1926	55	Right wrist	9 years	+ (fall on wrist)	+	Few
7. Mrs. G. ..... May, 1926	42	Right third finger	2 years	0	+	+
8. Mrs. C. G. ..... February, 1927	26	Right thumb	1½ years	0	+	+

Cholesterol determinations (normal: from 140 to 170 mg. per 100 cc.)

Case 5	96 mg. per 100 cc.	
	98 mg. per 100 cc.	Method: Meyer with naphthol green standard
	131 mg. per 100 cc.	Method: Meyer with cholesterol standard
Case 6	165 mg. per 100 cc.	Method: Bloor with cholesterol standard
	143 mg. per 100 cc.	Method: Bloor with cholesterol standard
Case 7	185.3 mg. per 100 cc.	Method: Bloor with cholesterol standard

Recurrences: none to date.

Average time since operation, 4 years, 4 months
Longest time since operation, 8 years
Shortest time since operation, 6 months
(Case 8 excluded)

Treatment: Local excision in all but case 2
Case 2: amputation of finger after frozen section was diagnosed as giant cell sarcoma

* Features to be noted are the predilection of the tumor for the right hand, the long duration of the tumor in cases 1 and 6, the frequency of trauma (five times in eight cases), the normal cholesterol figures in cases 5, 6 and 7, the absence of recurrence in all cases. Treatment in all cases consisted of local excision, except in one case which was diagnosed as giant cell sarcoma on frozen section.

We have collected from the literature the records of 144 cases of tumors of the tendon sheaths and fibrous tissues of the extremities, some of them with complete data, others with less information. Table 2 gives the authors and the number of reported cases. While we do not claim that this is a complete list of all recorded cases, we do think that it is sufficiently large to warrant certain conclusions.

Etiology.—The etiology of this condition remains obscure. There is no agreement among authorities as to its actual pathology, and consequently its true nature is in doubt. Sex seems to play a slight rôle.

Of 122 cases in which the sex is recorded the women outnumber the men by 68 to 54, a proportion of about 55 per cent women to 45 per cent men, certainly not a decisive figure. Age also plays some rôle, the condition usually occurring in adult life. No age, however, is immune: Paviot and Albertin reported a case in a boy, aged 9; Mencière reported one in a girl of the same age, and Garrett reported that one of his cases of fibroma of the tendon sheath appeared at the age of 5. Reverdin saw such a tumor in a woman of 83, and Fritsch reported one in a man of 73. In one of Fritsch's cases the tumor had been present since birth. The average age in the 122 cases is 35 for the women and 39.9 years for the men. Broders gave 47.2 years as the average age for his patients, and ours also seem to be somewhat older.

TABLE 2.—*Sources of Reported Cases of Giant Cell Xanthomatic Tumors*

Name	Date	No. of Cases	Name	Date	No. of Cases
Broca	1860	1	Bellamy	1901	5
Czerny	1869	1	Heller	1902	4
Paquet	1878	1	Martini	1902	1
Gross	1878	1	Malapert and Morichau-Beauchant	1905	1
Dennucé	1885	1	Coenen	1905	6
Reverdin	1885	1	Bazy	1907	1
Mayer	1886	1	Gaudiani	1908	1
Labougle and Cassaet	1890	1	Fritsch	1908	2
Heurtaux	1891	3	Lenzi and Abetti	1909	7
Reboul	1892	1	Russel	1911	1
Pilliet	1893	1	Hedinger	1912	4
Pilliet and Maucleire	1894	1	Beekman	1915	3
Longuet and Landel	1895	1	Stewart and Flint	1915	2
Malherbe	1896	2	Pybus	1917	1
Bonhomme	1897	1	Ely	1918	1
Bonjour	1897	1	Broders	1919	17
Wagner	1897	1	Kaufmann	1922	3
Targett	1897	2	Seyler	1922	8
Venot	1898	1	Buxton	1923	2
Dor	1898	1	Garrett	1923	30
Mencière	1898	1	Dyke	1924	2
Albertin and Paviot	1899	1	Weber	1924	1
Arcoleo	1899	1	Miller	1924	1
Delbance	1900	1	Harbitz	1925	7
Mueller	1901	6			
Tomaselli	1901	1			

Duration.—The duration of the growth seems to be of no particular importance except to emphasize its benign character. The average duration in eighty cases was 4.3 years; Broders gave 7.6 years as the average in his seventeen cases. Some had been present from eighteen to twenty years before they were removed, and in the case reported by Fritsch, the tumor had been present since birth and was removed at the age of 31. The tumor in one of our cases had been present for nine years. The duration of the growth does not seem to bear any particular relation to the size. A tumor of from one to two years' duration may attain in that time the size of a walnut or of a hen's egg, while one of many years' duration may be no larger than a cherry.

Trauma seems to be an important factor in many instances. Dennucé's tumor was ascribed to a blow. One of Heller's patients was a

coiner, and the growth was attributed to his occupation. One of Fleissig's patients was a seamstress, and the tumor occurred on the left hand at the point where the needle was accustomed to prick after being stuck through the cloth. Another of his patients stuck the finger with a fork, and the tumor developed at this point. Beekman reported a case in which the tumor was thought to follow some injury at golf. Stewart and Flint record an instance in which the tumor developed after a fall. Ely records one after repeated falls on the ankle. Broders reports a history of trauma in six and of infection in two of his seventeen cases. Delbance's patient was neurotic and rubbed his thumb against his teeth, and the tumor developed at this place. Of our patients, five had a history of trauma—a rather high percentage. It seems to us that trauma may play a rôle and that it is present more often than the statistics show, and we are inclined to agree with Broders and Garrett that it is an important factor.

TABLE 3.—*Age and Sex Distribution and Incidence of Trauma in 122 Cases of Xanthoma*

Sex: men, 54; women, 68

Age	Female	Male
0 to 10	1	1
11 to 20	8	5
21 to 30	18	8
31 to 40	9	9
41 to 50	7	7
51 to 60	6	8
61 to 70	3	4
71 to 80	0	1
81 to 90	1	0

Average age: females, 35; males, 39.9. Youngest, 5 years; oldest, 83 years

Average duration in 80 cases	4.3 years	(Broders 7.6 years)
Longest duration	31 years	
Shortest duration	6 weeks	

Trauma, 10%; Garrett, 30% probably; Broders, 30%; personal, 60%

As to occupation, there is no agreement; some authors think that laborers are more frequently affected, though this has not been definitely shown.

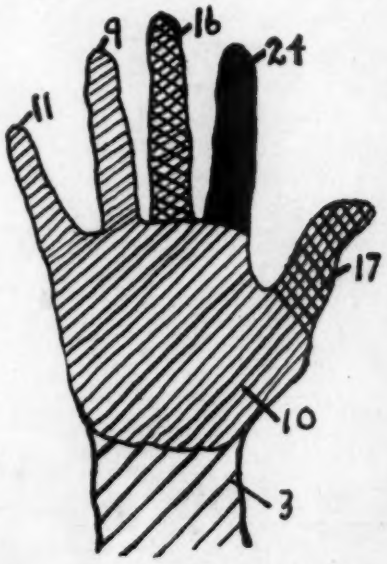
Table 4 shows that in 123 collected cases, ninety-six tumors occurred on the upper extremity and twenty-seven on the lower. Of the ninety-six on the arm, fifty-eight were on the right and twenty-eight on the left hand, while in ten cases this distinction was not reported. The incidence for the separate fingers is shown in the diagram: Of ninety tumors, twenty-four were on the index finger, seventeen on the thumb, sixteen on the middle finger, eleven on the little finger, ten on the palm, nine on the ring finger and three on the wrist. Of seventy-four tumors, fifty-nine were on the flexor surface, ten on the extensor surface and five on both flexor and extensor surfaces. On the lower extremity the right is also the most frequently affected, and here the region of the

malleoli, especially the external, is more often the site of the tumor. It appears to us that the fact that the tumor appears more often on the hand, and on the fingers of the right hand, and on the fingers of this hand that are most subject to trauma, certainly indicates that trauma is a factor in its growth.

The question of hypercholesterinemia in the xanthomas has been especially emphasized since the work of Kawamura and of Pinkus and Pick demonstrated that this was the substance that filled the foamy cells and that in many cases in which there were such tumors there was an increase of this constituent of the blood. In many instances of xanthoma

TABLE 4.—*Location of the Giant Cell Xanthomatic Tumors* *

Upper Extremity, 96	Right, 58	Left, 28	?, 10
Wrist	1	2	0
Palm	8	2	0
Thumb	10	4	3
Index	15	8	1
Middle	11	5	0
Ring	7	2	0
Little	5	4	2
Finger	1	0	3
Forearm	0	1	0
Over ulnar nerve	0	0	1
	Flexor	Extensor	Both
Surface (74 cases)	59	10	5
Lower Extremity, 27	Right, 14	Left, 4	?, 9
Ankle	8	0	4
Great toe	0	0	0
Second toe	2	0	0
Third toe	1	1	0
Fourth toe	0	0	0
Fifth toe	0	1	0
Foot	2	0	2
Leg	1	0	3
Thigh	0	2	0



* The upper extremity is by far the most frequent site for these tumors and especially the right hand. The frequency of the separate fingers is shown in the diagram.

multiplex, lesions are found in the tendon sheaths that are similar to the isolated tumors, and from this it has been argued by many that the isolated tumors are also associated with an increase in the blood cholesterol. The evidence is, we think, only inferential and is not supported by direct proof. Certainly in those of our cases in which cholesterol determinations were made, no such increase of the blood cholesterol was found. Some instances of xanthoma multiplex are reported in which high blood cholesterol was not present (Rosenthal and Braunisch, 1921). We are not inclined to look on the isolated tumors as being associated with hypercholesterinemia.

The ideas concerning these yellow tumors have undergone many changes since attention was first directed to them by Rayer and Lebert. Following the lead of Nelaton, most of the early authors classed them with tumors arising from bone marrow and assumed that they arose either directly from medullary substance or from misplaced bits of bone marrow substance. Paget described these tumors, and although he notes that they may come from many other than osseous tissues, he does not seem to doubt that myeloma is the correct name for them. Czerny, who likened the tumor he described to an epulis, thought, however, that the tumor might arise from connective tissue and that the wandering cells might play an important rôle. Gross also seconds many pathologists of his time in the opinion that these tumors are not of osseous origin and that the giant cells may easily arise from the soft tissues as well as from bone. It is hardly a moot point at present; it has been well established that in the vast majority of cases giant cells are probably the response of the organism to foreign material or to certain types of infections and that their presence usually means this and nothing more.

The moot points at present concern the question of the neoplastic or inflammatory nature of the growth and the relation of the isolated growths to increased blood cholesterol. Dor, in 1898, noted the presence of the giant cells in the xanthomatic tumors and the presence of xanthoma cells in the myelomas, and stated that "il existe un état morbide local identique capable d'engendrer suivant des tissus tantôt des myelomes, tantôt des xanthomes, et quelquefois des myelo-xanthomes." He thought the tumor was inflammatory in origin and was about the first to suggest such an origin for it. Although the majority of writers before and after him have assumed that the tumor is sarcoma, his views are gaining ground, and, considering the clinical course along with a rather puzzling type of pathologic picture, one is surely justified in assuming that it is not sarcomatous. If the growth is a sarcoma, it is by definition malignant, and if it is not malignant, it cannot be a sarcoma. The medical profession seems to be in the same predicament about this growth as it was about the giant cell tumors of the bone a few years ago. It is pretty well agreed that these tumors are not malignant. Any one who has studied the histories of a series of these cases must agree that the growths are benign, even though they may resemble histologically certain malignant growths. Whether one should accept the opinion of Dor, Fleissig, Broders, Seyler and others and assume that they are inflammatory (Seyler favors calling them granulation tissue tumors) is a difficult point to answer. If not, then one may assume with Levy that they are benign tumors of the reticulo-endothelial system, i. e., histiocytomas. Certainly there is nothing in the growths that is not compatible with granulation tissue, and although the picture is not that

usually seen in granulation tissue, all the elements present may be found in granulation tissue, and the assumption may not be so far wrong. We are rather inclined to look on these tumors as inflammatory and not neoplastic.

Gross Pathology.—The size to which the tumors may grow does not bear any relation to their age. They are somewhat larger on the ankle than on the hand and larger on the wrist than on the fingers. Most of them are about the size of a hazelnut or walnut, although many have been described as much larger; they have been reported as large as a goose egg on the thumb, the size of a hen's egg on the palm and the size of a pigeon's egg on the middle finger. One in our series which was thought to be tuberculous would have filled a 6 ounce bottle.

Site of Origin.—Not all of these tumors take their origin from the tendon sheaths, although they are usually accredited to this tissue. Garrett, in studying 196 tumors of a rather common pathologic make-up, found 135 of the same type; that is, they belonged to the xanthoma group. When these tumors are on the hands or feet they most often come from the tendon sheaths, but even here many take their origin from subcutaneous tissue or other fibrous tissue. Some tumors of the joints have the same pathologic picture as xanthomas of the tendon sheath. Gross, Ferre and Targett reported instances in which the tumor arose from the palmar fascia. In the cases reported by Stewart and Flint, one had taken its origin apparently from the volar carpal ligament. Longuet and Landel reported a tumor coming from the fibrous capsule of the talocalcanean joint. In one of Broders' cases, the tumor had taken its origin from the fascia of the leg. Corten's tumor had come from the subcutaneous tissues of the thigh (not from the fascia lata). In a case reported by Seyler (1922), the tumor had grown about the ulnar nerve, which was easily shelled out from it. It had probably come from the perineurium. In some instances the tumor seems to have had an osseous origin, or at least tumors of similar type some from the bone (Dyke, Ely).

In our cases, the tumor came from the tendon sheath twice, from the palmar fascia once, from subcutaneous tissues three times and from fibrous tissue about joint or bone twice.

Color.—The tumors are frequently compared grossly to suprarenal tissue. They present a variable mixture of yellow and brownish red, in a gray connective tissue capsule that often sends down into the tumor strands of fibers which divide the tumor into lobules, giving it the appearance of marble. The reddish elements are due to the presence of blood or blood pigments in the tumor, following the frequent hemorrhages which are characteristic for the growth. The pigment gives the Berlin Blue reaction for iron. The yellow comes from carotin and

xanthophyll (as E. M. Miller suggested), and not from cholesterol, as is commonly supposed, since cholesterol is colorless. The typical coloration may be entirely lacking, and still the growth may be indistinguishable from other xanthomatic tumors; on the other hand, all tumors with this peculiar coloration are not necessarily xanthomas.

Consistency.—The tumors are tough and elastic, cut across like fibromas, and the hardness combined with the color is enough, according to Bloodgood, to make the gross diagnosis. They vary in their consistency; some are hard, as was one reported by Beekman which had the consistency of a cartilaginous tumor. Some contain so much iron that they have to be treated with oxalic acid before they can be sectioned. Others are soft and may feel like lipomas. In one of our tumors the consistency resembled that of a giant cell tumor of bone.

On section they present a capsule of varying thickness, which sends trabeculae down into the tissue, dividing it into lobules of mixed reddish brown, yellow and gray. Blood vessels may or may not be numerous, and the lobule may or may not project above the surface of the cut section.

They are smooth and rounded, usually lobulated, consisting of one large lobule with several smaller ones from its surface. The tumor is frequently composed of a number of separate lobules held together by threads of connective tissue. They are more often elliptical than spherical, spreading out along the side of the finger.

Microscopic Picture.—In describing the minute picture of these tumors, we find that they are a great deal like the facetious definition of exophthalmic goiter, which is characterized by neither exophthalmos nor goiter, for these tumors may lack either giant cells or xanthoma cells; but they always possess one or the other, and in the great majority of cases both types are present. They seem to be a clinicopathologic entity rather than a pure pathologic entity. The description may be divided into descriptions of the capsule, the stroma, cellular elements, vascular elements and pigment. The possibility remains that one is dealing not with one tumor, but with several having many things in common.

The great diversity of cellular elements is their most striking characteristic. This has led to a great deal of trouble in their classification. They usually possess a connective tissue capsule (fig. 4 *A*) which sends down fibrous septums into the tumor (fig. 6 *A*), dividing it into lobules (figs. 6 *A* and 5 *B* and *C*). These septums are frequently made up of adult connective tissue, not infrequently of fibroblasts (fig. 4 *C*); at other times they become hyaline and contain few or no cells (fig. 5 *B*). At times the septums are absent or scarce, and the tumor is cellular; at other times they may be so numerous and so well developed

that the growth takes on the appearance of an alveolar sarcoma (fig. 5 *C*). The tumor may be cellular in one part without any septums, while in other places it is distinctly alveolar.

The most frequently described cell is a spindle cell (fig. 5 *A*), and many authors have given the name of spindle cell sarcoma to the growth. Paget described the cell in his early description, as did Paquet, Heurtaux, Targett, Coenen, Gaudiani, Pybus, Ely, Kirch, Seyler, Garrett, Levy and many others. We found it in all of our tumors, frequently in great abundance, suggesting sarcoma (fig. 5 *A*). Apparently, a great many of these cells are fibroblasts which result from connective tissue proliferation and are certainly not sarcomatous.

Endothelial cells are found usually in large numbers. They have a reticular cytoplasm (fig. 6 *B*) and show evidence of developing into foamy cells. They are especially abundant in tumors which show evidence of vascular proliferation, and it seems that at times we can trace the cells from the endothelial lining of blood vessels (fig. 12 *A, B* and *C*). They may also come from other cellular elements of the reticulo-endothelial system. They are frequently filled with pigment when it is present in the tumor (fig. 7 *B*). The same may be said for the spindle cells, which may also take up pigment, showing them to be capable of phagocytosis. Both these cells (endothelial and spindle) may well be inflammatory in nature.

Various other cellular elements are described in these tumors. Perivascular round cell infiltration (figs. 7 *A* and 15 *A*) is not infrequent and was seen in nearly all our tumors, although this is usually not a marked feature. It may not be present in all parts of the growth, but only in a few places. Polymorphonuclear leukocytes were noted in rare instances; at one time, in the first tumors removed from Mother A., there was a general infiltration of the tumor with eosinophils. At the second operation they were again sought, this time in vain. Other types of polymorphonuclears were infrequently seen, never in any abundance. In the sinuses that will be described later, leukocytes were seen in a higher percentage than one would normally expect (fig. 15 *A* and *B*). Other infiltrating cells present include large mononuclears, with oval or bean-shaped nuclei, many times full of pigment (fig. 10 *A* and *B*). They belong to the reticulo-endothelial system, having to do with the resorption of the products of red cell destruction or the removal of other products of cellular degeneration. Red blood cells are often seen in the tissues, sometimes perivascular; at other times only the masses of pigment remain to show where a small hemorrhage has occurred. These collections of red cells were numerous in some tumors; in others they were rare; in some tumors the hemorrhages could be found only at the junction of the capsule and the tumor proper.

The foamy cells and the giant cells are the most striking components of the tumors, but they are not present in all of them. In our series the foamy cells were seen in all but one tumor, and giant cells were seen in all of them; in one, however, they were so rare that they were almost missed. The foamy cells (figs. 8 *A* and *B*, 9 *A* and *B*, 10 *A* and *B* and 14 *B*) are large polyhedral cells with small pyknotic nuclei which may often be multiple (from two to three to a cell). The cytoplasm is vesiculated, the vesicles being nearly all the same size and separated from each other by granular cytoplasm. The cells are separated from each other by a sort of connective tissue reticulum in which connective tissue nuclei are seen. On staining with sudan III the cells are seen to be filled with a fatty substance, which with osmic acid stains gray and shows itself to be a lipoid. With polarized light the vesicles of the foamy cells are seen to contain a doubly refractive substance that may be proved chemically to be cholesterol. The foamy cells are present in groups of a few cells (fig. 10 *A* and *B*) or as large masses which form a considerable part of the tumor. In other instances the foamy cells may occur as isolated groups of eight or ten cells, not often as single cells. When they are present as large masses they may be distinct from the rest of the tumor (fig. 9 *B*). At first glance one might be inclined to think that they were definitely separated from the rest of the tumor; on closer inspection one can see that the boundary is nothing more or less than the simple juxtaposition of the two cellular fields with no tissues between, and that even where the line seems to be distinct the gradual vesiculation of the neighboring cells and the formation of foamy cells from them may be seen. The foamy cells can be traced from both the endothelial cells and the fibroblasts, and may be confined to the periphery of the tumor, or they may occur in all parts of the tumor. In the case of Mother A., no foamy cells were seen in the tumor removed from the cavity of the joint, but some were found in the tumor which had invaded the carpal bones. In the tumor in case 4, none was seen, though the giant cells were abundant. In one case in which the foamy cells were not especially abundant, several foamy giant cells were seen (fig. 11 *C*). The significance of the foamy cells is a moot question. It has been well established that they contain cholesterol, which causes their foamy appearance, but just why they should appear in this type of tumor is not known. The suggestion that there has been an increased blood cholesterol is not proved, and it must be assumed that the cells are taking up cholesterol formed as a result of the tissue degeneration. It seems likely that any cell taking up cholesterol will assume the foamy shape and that this is the only significance of these cells. It seems to us that they are most frequently derived from the endothelial cells; many

stages of gradation from the endothelial cells can be seen. In other instances they are derived from fibroblasts.

The giant cells are the next prominent type found in the tumor (figs. 4 *A, B* and *C*, 6 *A* and *B* and 11 *A, B* and *C*). They were seen in all of our tumors, their number, however, being variable. In some of the tumors they were as numerous as similar cells in giant cell tumors of bones; in others they were as rare as they were formerly abundant. They were of every conceivable size, shape and nuclear arrangement. Many resemble the Langhans giant cells; many were small and contained only a few nuclei; others were large, assuming enormous size and containing nuclei numbering in the hundreds. The nuclei may be arranged as a peripheral circlet or as a central circlet; they may be scattered throughout the whole cell or at one end or bunched up in the center. Many are filled with foreign particles and detritus or contain cholesterol (fig. 11 *C*). The giant cells seem to be produced from the fusion of many endothelial cells or to bud off from the endothelial cells of the proliferating vessels, where they may be seen projecting into the lumen (fig. 13 *A*). They do not seem to bear any particular relationship to the foamy cells; in fact, few giant cells are seen in the foamy cell groups, and where the giant cells are numerous, the foamy cells are not abundant. The giant cells are not infrequently loaded with pigment; if so, they are smaller than the cells which do not contain any pigment. Foamy giant cells were noted in one tumor (fig. 11 *C*). Where giant cells are numerous, they so pack the tissue that one thinks of a giant cell bone growth (fig. 4 *A*). In some sections the cells were so arranged as to suggest an alveolar sarcoma (fig. 6 *A*). In the case of Mrs. G., their arrangement suggested the location of vessels which had undergone endothelial proliferations, with the resultant formation of giant cells (fig. 13 *B*). In the case in which invasion of the bone was seen (fig. 16 *A* and *B*), surprisingly few giant cells were found.

The blood vessels of the tumor are also variable (figs. 7 *A* 13 *A* and *B*, 14 *A, B* and *C* and 15 *A* and *B*). In many the vessels have extremely thin walls, are numerous and are apparently normal. They may be extraordinarily numerous, or they may be scarce. Two vascular changes are worthy of note; the endothelial proliferation and the presence of sinuses. The histologic picture of endothelial proliferation was given by Bellamy in 1901. The whole general question of the proliferation of the common vascular endothelium has been considered by those studying the reticulo-endothelial system, and there is still lack of agreement among authorities as to whether the endothelium of the ordinary vessels can give rise to phagocytic cells. Mallory and his school believe that the common vascular endothelium may give rise to various cells that wander out into the tissues in response to various

stimuli, as infection, foreign bodies, etc. Aschoff and his pupils and Sabin and her followers do not believe that the common vascular endothelium belongs to the recticulo-endothelial system. It seems to us that settlement of this question might be important in the classification of these tumors. The changes interpreted as endothelial proliferation have been noted in many of our cases. At times such changes were numerous; almost every field showed the thickening of the vessel wall, the fattened endothelial cells, the increase in numbers of these cells and the formation of cells which project out into the lumen of the vessels or which seem to grow outward into the surrounding tissues (figs. 12 *A, B* and *C* and 13 *A* and *B*).

The presence of sinuses was noted in many of these tumors (figs. 14 *A* and *B* and 15 *A* and *B*). These sinuses, some vascular and some lymphatic, have led many to call the growths angiomas. At times the sinuses are among the foamy cells (fig. 14 *A* and *B*), and at other times in the endothelial cell groups. They may be numerous in some parts of the tumor and missing in others. In the second tumor of Mother A. (fig. 15 *A* and *B*), they were plentiful and were filled with blood.

Pigment was present (fig. 7 *B*) in all of our tumors. It was for a large part iron-positive, giving the Berlin Blue reaction, and came without doubt from the destruction of the extravasated red cells. The pigment is mainly intracellular, being taken up by the endothelial cells, by fibroblasts, by the giant cells and by certain large mononuclear cells which may be clasmatocytes. The pigment is not evenly distributed throughout the tumor, but is more abundant in some areas, others being free from it. In some tumors it lies at the periphery, under the capsule. In some tumors it had a sort of perivascular arrangement.

As to evidence of malignancy, the question in our minds is settled, not by the pathologic picture alone, but by a consideration of the clinical picture along with it. Most authors (there are a few exceptions) agree that the tumor is benign and that it should not be called a sarcoma. An analogy may be made with the giant cell tumor of the bone, which has many things in common with this tumor. However, there have been some cases of giant cell tumor of the bone which were reported as giving rise to metastases (Kolodny, and Finch and Greave give literature on additional cases). In two instances malignancy was suggested to us. In one the capsule in certain spots seemed to be invaded by the tumor cells, and in the other the carpal bones were invaded. No other evidence of malignancy was noted, and it may be that in regard to invasion of the bone the suggestion of Broders' is correct—that the presence of the giant cells, which are bone absorbers, may have led to the destruction of bone, or, as we suggest, the pressure of the tumor on the bone may have led to necrosis. The capsular infiltration is a different matter. Suffice it to say that no other evidence of malignancy was seen, there

was no lymphatic enlargement, and the course of our patients to date, as well as of all those from the literature, does not indicate malignancy.

Symptoms.—The clinical picture of this growth is simple. The onset is insidious, with a small tumor which the patient may or may not attribute to trauma or to infection. It is of slow, insidious growth and on the finger seldom reaches a size over that of a hazelnut. It causes little or no trouble and when on the hand rarely gives rise to pain; on the foot it is frequently associated with pain. Rosenthal says that on the foot the growth is always associated with pain. None of the tumors in our cases were on the foot, but from the literature one does not get the impression that all on the lower extremity caused pain. There may be some functional disturbance from the size of the tumor. They may interfere with putting on gloves; on a dentist's or a surgeon's hand they may cause trouble in the handling of instruments. If low on the finger they may be subject to trauma from a ring. One of our patients, Mother A., complained of tingling and burning in the wrist and fingers. In one of Bellamy's cases the tumor came on two days after sudden causeless pain.

One characteristic that should be emphasized is the tendency to sudden accession of growth which these tumors may show. They may grow along slowly for several years and then start in rapidly to enlarge. In a case of Paquet's in which the tumor had been present for twelve years when operation was performed, it had reached the size of a pea at the end of ten years; it then started to grow, and after two more years had grown to the size of a walnut. A sudden accession in growth does not necessarily mean that the growth is malignant. Trauma may lead to more rapid growth. Ferre's patient said that after starting arms practice the tumor grew more rapidly, and in the case of Pilliet, the tumor, which had been quiescent for many years and which had been present since birth, started in to grow after it had been punctured, with the recovery of some blood. In a case of ours, the tumor began to grow suddenly eight years after the onset. In this same case, after removal of the volar mass, there was a sudden causeless pain with swelling and redness, which, however, subsided later.

One point to be noted on examination is the consistency of the growth, which is about that of a fibroma, elastic and at times tense and pseudofluctuant. It does not have the hardness of an osteoma or of a chondroma. As a rule, the skin is movable over it, and the tumor can be moved over the tendons and bones. Rarely is the skin attached to them, and they ulcerate only if surgical treatment has been applied and infection introduced. Lymphatic involvement never occurs.

Diagnosis.—Xanthomas are among the most common tumors of the finger. A solid growth, movable under the skin and attached to the bone, is in a large number of cases a xanthoma. It should be differ-

entiated from the chondroma, which is harder than the xanthoma; from lipoma which is softer; from the carcinoma, which affects the skin; from the osteoma, which is harder and is connected with the bone. A ganglion is smaller and is usually on the extensor surface. Tuberculosis of the tendon sheath may be difficult to differentiate, as was noted in one of our cases, in which the growth was at the wrist on both volar and dorsal surfaces and was thought to be tuberculous before operation. Fibromas of the tendon sheaths occur, but they are rare. Tumors of muscle or of tendons are rare, but should be thought of. Tenosynovitis and tuberculous dactylitis are possibilities. One case reported by Fleissig was considered a panaritium at operation.

Prognosis.—Metastases did not occur in any of the cases found in the literature or in any of our cases. No authentic cases of death from a giant cell xanthomatic tumor of the finger have been reported in the literature, so far as we can ascertain. A definite tendency to recurrence has been noted many times by all who have written concerning this tumor. The percentage of recurrence is, however, not high (10 per cent). In the case reported by Gross, the tumor recurred three times in three weeks after operation, but after removal of each growth it finally healed and had not recurred a year after the last operation. In one of Heurtaux's cases the growth recurred six months after first removal and was locally excised again and remained cured. The tumor in Bonhomme's case recurred. Three of the tumors reported by Targett recurred, but evidently none of the patients died from the growth. In Tomaselli's case the tumor began to grow rapidly two years later, and the foot was amputated. The tumor in Martini's case also recurred, and was removed a second time; the patient was cured. One of Fleissig's patients had a recurrence of a tumor that had been removed three years before. Garrett reported five recurrences in thirty fibromas of the tendon sheath.

Treatment.—The treatment of this tumor has become well established. Its resemblance to sarcoma has led many to advise a mutilating operation for a relatively harmless condition, however, and probably many fingers have been sacrificed because of this confusion. Fortunately, it is not a frequent condition. It is well agreed that local excision or enucleation, as in other types of benign growths, such as lipoma or fibroma, is all that is required. Even when it recurs, as it does in a certain percentage of cases, the new growth should again be removed, and the finger or hand should not be amputated. It should be treated usually in the same fashion as giant cell tumors of the bone.

The tumors usually shell out easily and are encapsulated, at least in the early stages, though later the encapsulation is lost. The origin from the tendon sheath is often recognized, and this fact should lead

the surgeon to think of xanthoma at once, as this is by far the most frequent tumor of the tendon sheath. When the growth is removed, the tendon is not infrequently laid bare. The gross appearance of the tumor is also suggestive, and when the origin and consistency are considered, it makes an almost pathognomonic picture. They tend to be the size of hazelnuts and are lobulated on the surface, so that they often appear to be made up of a conglomeration of several lobular masses; at times the fibrous strands from the capsule are seen to divide the surface up into lobules. The same lobulation can be seen on the cut surface, the trabeculae running from the capsule down into the tumor. The tumor is firm, with about the consistency as that of a fibroma. Usually, the cut section of the tumor is solid—cysts are rarely found in it. The lobules are of different colors, the most prominent color being yellow, varying from canary to a deep golden shade. The color accounts for the naming of the growths. Mixed in with these yellow nodules are other colored nodules, some of them being a dark red or reddish brown like a giant cell tumor of the bone. These areas on microscopic examination are usually found to contain the giant cells and are often loaded with a Berlin Blue positive pigment originating from blood. The area between the nodules is gray or white and microscopically is found to be connective tissue, young or old. The pigment may lead to misunderstanding, especially on microscopic examination, when it may cause confusion with melanoma.

On frozen section three characteristics should be looked for. The giant cells are of great importance. As Bloodgood remarks, if these are of the foreign body or epulis type, the diagnosis of sarcoma can be practically excluded. Xanthoma cells are also important, as their presence in the tumor excludes sarcoma. The pigment is important, as it gives the positive reaction for iron, and blood cells which give a clue to its origin are frequently found in the tissue. The pigment may lead to an erronous diagnosis of melanoma, unless the characteristics of its distribution are noted. Instead of regular distribution in the cells, it tends to appear in various-sized granules, many of which are as large as the nucleus (Smith, 1924). Some of the pigment is extracellular.

If the tumor recurs, it should be removed a second time, as in cases of giant cell tumor of the bone. Cases are reported in which the tumor has been removed three times, resulting in eventual cure without amputation. Recurrence is almost to be expected, unless great care is exercised in removal, and even then it takes place in a certain number of cases.

CONCLUSIONS

The giant cell xanthomatic tumors of the fingers and hands that occur as isolated growths are benign. They show some tendency to recur if incompletely removed, but they do not produce metastases.

Pathologically, they are polymorphic and may be confused with sarcoma, and they often have the appearance of endothelioma or angioma; but there is nothing in them that is not compatible with granulation tissue. We do not believe that there is any increase in the blood cholesterol in the isolated tumors. The right hand and certain fingers of this hand are most frequently affected, and trauma appears to be a frequent cause for the growth. They should be removed locally and do not require a mutilating operation for cure.

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MALIGNANT TUMORS OF THE TESTICLE

WITH SPECIAL REFERENCE TO CLASSIFICATION*

JOHN H. MORRIS, M.D.
Assistant Professor of Surgery, New York Postgraduate Hospital; Adjunct Visiting Surgeon, Fourth Division, Bellevue Hospital
NEW YORK

Invasion of the testicle by neoplastic disease is notably uncommon as compared to its occurrence in other parts of the body; explicitly, malignant tumors of this organ constitute less than 3 per cent of all the malignant growths encountered throughout the human body.

Despite this rarity, however, the unique and unusual features which characterize and distinguish these tumors, both structurally and clinically, have focused on them a degree of interest and study in striking disproportion to their observed incidence and have established their importance in medical literature.

Clinically, this condition is usually conceived of as a solid tumor of the testicle, often static for a considerable period, but eventually presenting characteristics of slow local growth, which is finally expressed as widespread general metastases. Variations from this sequence are not infrequently seen, however. The disease may be met first in the form of metastatic tumors of the brain, lung and abdomen in a young person in whom an apparently innocent testicular tumor, possibly of some duration, has suddenly initiated a process of general dissemination with little or no gross clinical indication of its altered rôle. In other instances, the sudden development of an abdominal or pulmonary tumor may lead for the first time to the discovery, during the course of a routine search for origin, of a testicular mass the benign appearance of which belies the offspring to which it has given birth. Startling and spectacular events of this nature are almost unparalleled in clinical experience and mark this disease as one of the clinician's most dreaded problems.

The structural features of these tumors present a different claim on the interest. From its inception, this phase of the subject has been responsible for a wide diversity of opinion concerning the nature and origin of malignant testicular tumors as well as their relation to embryonal structures of tridermal type found in the testicle.

The interest among pathologists and embryologists in the subject is attested by a voluminous literature, whose development has done much

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to dispel confusion and to standardize nomenclature. Discussion is still rife, however, regarding fundamental details of morphology and histogenesis, although the controversy has finally and definitely resolved itself into two schools of thought, each of which numbers among its adherents recognized eminent authorities and each of which advances important facts in proof of its contention.

Historical reference to the growth and evolution of the present theories throws some light on the underlying problems involved and justifies, in a measure, the irreconcilable difference of opinion which still exists.

The first recorded observation in this field seems to have been made in 1696 by Saint Donat, who described a rudimentary skull as a constituent of a testicular tumor. Subsequently, Proschaska, in 1803, and Perone, in 1833, made similar observations, noting the presence of fully differentiated tissues, such as hair, teeth and bones as elements of these tumors (Ewing). The real significance of these observations was made apparent only in 1856, when Johnson [1] identified in a solid, undifferentiated tumor of the testicle elements of all three primal germ layers in the form of bone, connective tissue and cysts lined by flat, columnar and ciliated epithelium. In 1887, Langhans, carrying on from this point, classified many tumors hitherto called pure carcinoma, alveolar sarcoma, etc., (i. e., unicellular) as of tridermal or teratogenous origin and further proposed that a large proportion of testicular tumors were of this nature. Wilms [2] made further advance in 1896 by classifying all complex tumors of the testis as teratogenous and by extending this grouping to include many structures previously classed under a varied terminology. He approached some degree of standardization by his classification of these mixed tumors under two heads, viz:

(1) Embryomas, which are large cystic tumors with an intracystic projecting tumor mass made up of fully differentiated tissue approximating the orderly arrangement of fetal rudiments. These tumors, whose tissues are of the adult type, are comonly called dermoids, are extremely rare and are usually of benign character, clinically.

(2) Embryoid tumors or teratomas, which are solid tumors comprising elements of all three primal germ layers, undifferentiated, embryonal and devoid of orderly arrangement.

The first group is of little clinical interest because of its benign character and its extreme rarity. The second group, on the other hand, exhibits structural and clinical features of peculiar interest. It was observed (Wilms,[2] Pick, Chevessau [3]) that there was a marked tendency

1. Johnson: Cystic Disease of the Testis in an Infant and Probably Congenital, Tr. London Path. Soc. **1**:241, 1856.

2. Wilms: Embryone u. embryoide Tumoren d. Hodens, Deutsche Ztschr. f. Chir. **49**:1, 1898.

3. Chevessau: Tumeurs du testicule, Thèse de Paris, 1906.

on the part of these mixed, undifferentiated tridermal tumors for one element or germ layer derivative to assume aggressive activity and to overgrow or suppress accompanying elements with the eventual production of what appears to be, on casual study, a pure, homologous or monodermal structure. Viewed in this light, many tumors previously regarded as pure, unicellular adenomas or carcinomas presented, on careful search, unmistakable evidence of suppressed elements, thus establishing their original tridermal nature.

Obviously, this conception extended the scope of the tridermal or teratogenous tumors to include many so-called homologous tumors hitherto placed under a variety of nomenclatures, and some authorities were inclined, at this point, to accept this origin for all malignant epithelial tumors of the testicle, regardless of their homologous or heterologous structure.

On the other hand, Chevessau,[3] who was among the first to recognize the principle of monodermal predominance in tridermal tumors and who accepted the teratogenous origin of many so-called homologous structures, was more conservative in the application of this principle. There still remained outside of the tridermal group, in his opinion, a large number of testicular tumors (estimated as about one-half) whose cellular morphology suggested another origin and in which no evidence of suppression could ever be detected, i.e., true homologous structures.

This particular tumor, which thereupon assumed a prominent place in the discussion, was described as medullary, cellular and with scant reticulum. The cells themselves were large, round or polyhedral, with large vesicular nuclei and presented, according to Chevessau, a picture identical with that found in the spermatocytes of the spermatogenic cycle. He therefore chose to regard the adult cells of the seminiferous tubules as precursors of these tumors and proposed for them the significant term of "seminome."

This theory of origin of this common and much discussed tumor of the testicle was generally confirmed and accepted by many competent observers subsequently. Thus two main classes of testicular neoplasms were determined, differing essentially in cell morphology and histogenesis: (1) the embryonal, distinguished by their heterologous, atypical structure and embryonal origin and (2) the simple, homologous, unicellular growths arising from fully differentiated adult tissues.

As recently as 1921, Schultz and Eisendrath,[4] in a review of a series of fifteen cases of malignant testicular tumors, classified nine as heterologous or atypical and six as definitely of the seminome type in which no evidence of heterologous tissues could be found. They accept the teratogenous origin of all heterologous tumors and include as well in

4. Schultz and Eisendrath: Histogenesis of Malignant Tumors of the Testis, Arch. Surg. **2**:493 (May) 1921.

this group all atypical adenomatous tumors, even in the absence of demonstrable heterologous elements. On the other hand, concerning the seminome type of tumor, they confirm in general the observations of Chevessau regarding the close morphologic resemblance between the cells of these tumors and those of the spermatogenic cycle, emphasizing, as further confirmatory evidence of the origin, a variety of nuclear forms observed in the tumors and identical with certain nuclear changes observed in definite stages of spermatogenesis. They consider this evidence ample to establish the origin of these tumors from adult seminal epithelium and, in view of their failure to demonstrate the presence of associated heterologous tissues in any single instance, to preclude the possibility of teratogenous relationship for these structures.

The stability of this conception of testicular neoplasms, as sponsored by Chevessau and others, is challenged by another school of thought, of which Ewing [5] is the leading exponent. The latter, in 1911, after making a careful analysis and study of a series of nineteen cases, arrived at conclusions which tended to simplify as well as to revolutionize preexisting ideas. His hypothesis is foreshadowed by a preliminary assertion that "Having seen the gradual inclusion of many apparently unrelated benign and malignant tumors of the testis into the single group of teratoma, suspicion arises that all or practically all testicular tumors may owe their origin to much the same embryonic disturbance." [6] In short, this hypothesis refers to a teratomatous origin not only those frankly mixed, heterologous tumors of the testicle but also homologous or apparently homologous tumors, benign or malignant, epithelial or mesoblastic.

Ewing is unwilling to accept an extrateratogenous origin of the common large-celled tumor; he places it definitely in the same group with the mixed tumors and submits convincing evidence in support of his contention that it represents a one-sided development of a teratoma. He points out that the sole justification for classing this tumor as a pure, homologous form is based on the failure to demonstrate heterologous elements, and that this is a faulty premise because these tumors are admittedly examined after they have become well advanced, when, according to the principle of predominance, ample opportunity has been afforded for complete suppression of slowly growing and scanty elements of the original structure. He therefore believes that failure to find teratogenous elements in a fully developed seminome is inadequate to disprove its teratogenous origin. Furthermore, regarding the significance attached to the reputed resemblance between the cells of this tumor and spermatogonia as a proof of origin, he recalls the fact that the cells

5. Ewing: Teratoma Testis and its Derivatives, Surg. Gynec. Obst. **12**:230, 1911.

6. Ewing: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922.

of the true adenomas of the testicle are quite unlike their precursors, and it is therefore difficult to explain why, in a more malignant carcinoma, the cells should revert to normal type. Finally, as the most convincing indication of the teratogenous relationship of these tumors, he demonstrates in one of his own cases the occurrence of characteristic seminome structure in combination with frank teratogenous elements.

Ewing therefore concludes that the data submitted do not satisfactorily prove that any considerable proportion of testicular tumors arise from tubules or stroma; on the contrary, he concludes that tumors of this organ belong to the embryonal class and that at least the majority of these embryonal tumors arise from teratomas.

Although this conception has not met with the prompt and general acceptance which its supporting evidence merits, it has at least stimulated a more careful study of the seminome tumor. But despite the renewed interest, Ewing's observations have met with but scant confirmation, and the majority of writers retain the seminome in the nonteratogenous classification. In 1923, however, Hinman, Gibson and Kutzman,[7] in an effort to clarify this disputed point, made a careful review of a series of seminome tumors and were able to demonstate, in one of them, mixed tissues of various types associated with the typical seminome structure. These writers thereupon revised their classification to include the seminome under the teratogenous grouping, thus corroborating the classification of Ewing. O'Crowley and Martland,[8] as a result of their study of thirteen cases of testicular tumors, expressed the opinion that for all practical purposes, there exists but one type of tumor of the testicle, viz., teratoma; but they submit no histologic evidence of the teratogenous nature of the seminome.

Therefore, in view of the fact that the nature and classification of the common malignant tumor of the testicle is still a matter of controversy, I take the liberty of presenting herein, as the basis of this report, data derived from a single case of teratoma testis in which the observations appear to offer a worthy contribution to the discussion. The case in question was recently encountered clinically after it had run the conventional course from focal tumor to visceral metastases. Death eventually followed from these visceral deposits. Subsequently careful postmortem studies, gross and microscopic, were carried out and interpreted under the direction of Dr. Paul Klemperer. The clinical and pathologic records follow.

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7. Hinman, Gibson and Kutzman: Malignant Tumors of the Testicle, Ann. Surg. **82**:552, 1925; Radical Operation for Teratoma Testis, Surg. Gynec. Obst. **37**:429, 1923.

8. O'Crowley and Martland: New Growths of the Testis, Surg. Gynec. Obst. **38**:486, 1919.

REPORT OF A CASE

History.—A young man, aged 24, was first seen in an acute emergency and gave a history of sudden onset of severe upper abdominal pain. Within twenty-four hours, the pains had become generalized over the abdomen, were colicky in character and were associated with persistent and uncontrollable nausea and vomiting. During the ensuing week, cathartics and enemas had been freely given but without result, the abdomen becoming gradually more distended and the patient progressively weaker and more emaciated owing to inability to retain food.

The patient said that for some months preceding this attack he had suffered from a chronic dry cough and "nervous indigestion." He said that he had never had robust health and that he had always been thin and underweight. He had been operated on by Dr. Oswald S. Lowsley one year before for tumor of the left testicle, following which his health had remained comparatively good until the onset of the present symptoms. This tumor was noticed only one month before operation, but during this interval had slowly increased in size; there was no history of injury. The patient had had mumps at the age of 15. He did not give a history of venereal disease.

Physical Examination.—On examination, he appeared pallid, emaciated and evidently acutely ill. The heart was normal, and no signs of a pathologic condition could be detected in the lungs. The abdomen was generally and tensely distended; free fluid could be detected in the flanks, and intestinal peristalsis was plainly visible through the thinned abdominal wall. General tenderness and rigidity precluded the possibility of detecting intra-abdominal masses. Rectal examination disclosed a distended ampulla and Douglas' pouch. The patient was in a desperate condition with rapid, low tension pulse and persistent vomiting of fecal type.

Operation.—An immediate operation was advised under diagnosis of intestinal obstruction and was carried out under local anesthesia. In view of the patient's grave condition, a rapid enterostomy was performed through the right lower quadrant incision, utilizing first the presenting loop of distended intestine. Although the enterostomy functioned well, evacuating intestinal contents and gas, the patient failed to respond and died twelve hours after operation.

Autopsy.—A summary of the relevant gross pathologic observations follows: In the abdomen an intestinal obstruction was found 15 cm. proximal to the ileocecal valve, at which point the ileum was found intussuscepted into itself, and at the apex of the intussuscepted loop there appeared a pedunculated tumor about the size of a walnut. The left lobe of the liver showed a walnut-sized tumor. A single large retroperitoneal lymphatic gland was noted at the level of the splenic flexure.

The lungs showed numerous tumors scattered throughout the parenchyma, varying in size from that of a cherry stone to that of an apple. On gross section, these appeared to be of two types; some were deep red and hemorrhagic, and some were white or mottled white. All were soft, with the exception of the one in the right upper lobe which was firm, white and cystic. Several large hilum glands compressed the esophagus in the mediastinum. The diagnosis at autopsy was: (1) multiple metastatic tumors of both lungs, left lobe of liver, mediastinal and retroperitoneal lymphatics, (2) pedunculated tumor of lower ileum with intussusception and intestinal obstruction.

Microscopic Examination.—The pathologic report on the primary testicular tumor removed from the patient one year previously, as obtained from the record through the courtesy of Dr. Oswald Lowsley, was as follows:

"The specimen consists of a globular mass of tissue measuring approximately 5.5 cm. in diameter. It is composed of the epididymis and a tumor of the body of the testicle leaving a crescent of about 1 cm. in thickness of

Fig. 1.—Metastatic focus in lung, showing island of cartilage.

testicular tissue at one pole. Cut section shows a brownish discolored surface with many cystic cavities filled with a somewhat viscid material. The more solid portions are grayish white and are the seat of irregular hemorrhagic foci. Section shows the picture of a teratogenous tumor with areas showing the characteristics of embryonal adenocarcinoma."

Metastatic Tumors.—Sections were obtained for study from the various pulmonary foci as well as from the solitary nodule in the liver, and typical sections

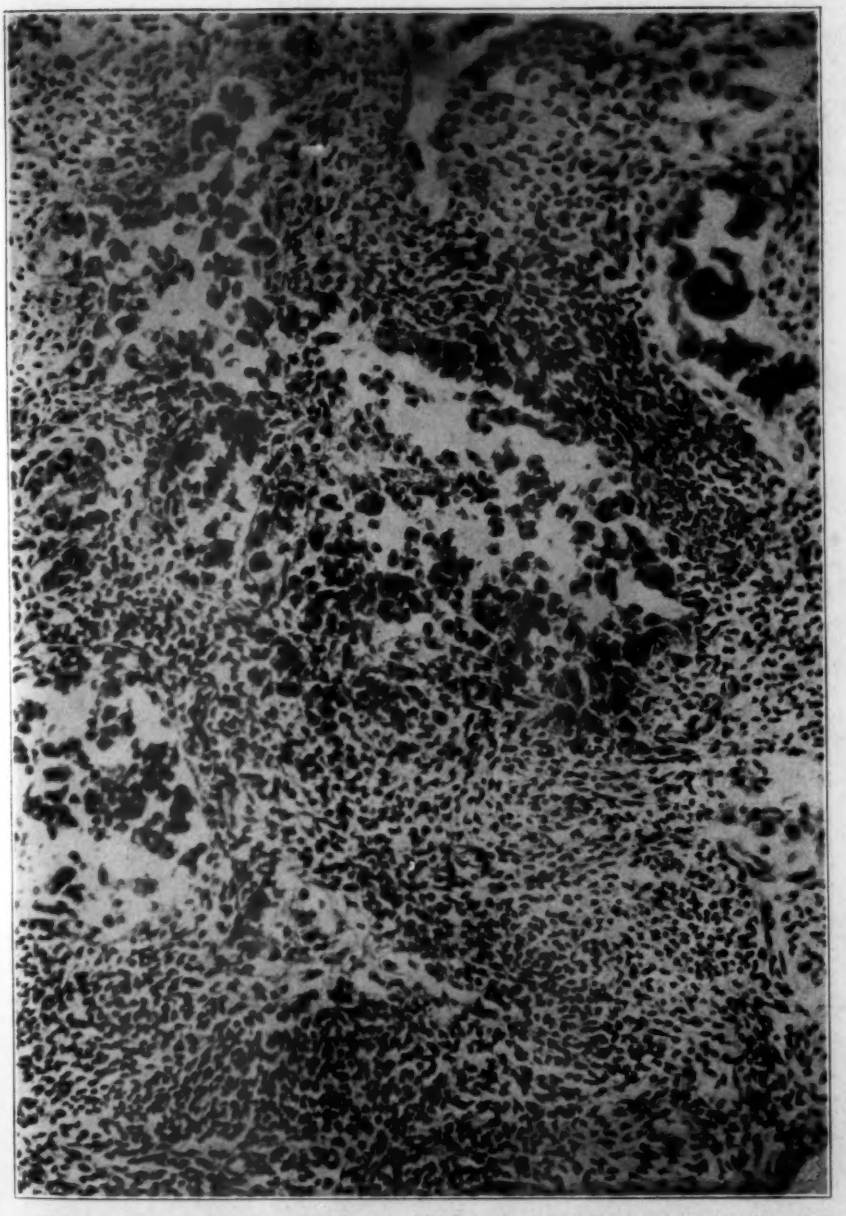

Fig. 2.—Metastatic focus in lung. Diffuse lymphoid stroma; cyst lined by columnar epithelium; areas of diffuse large round cells with vesicular nuclei.

Fig. 3.—Metastatic focus in the liver; multinucleated islands of syncytium and the large glycogen-holding cells of Langhans.

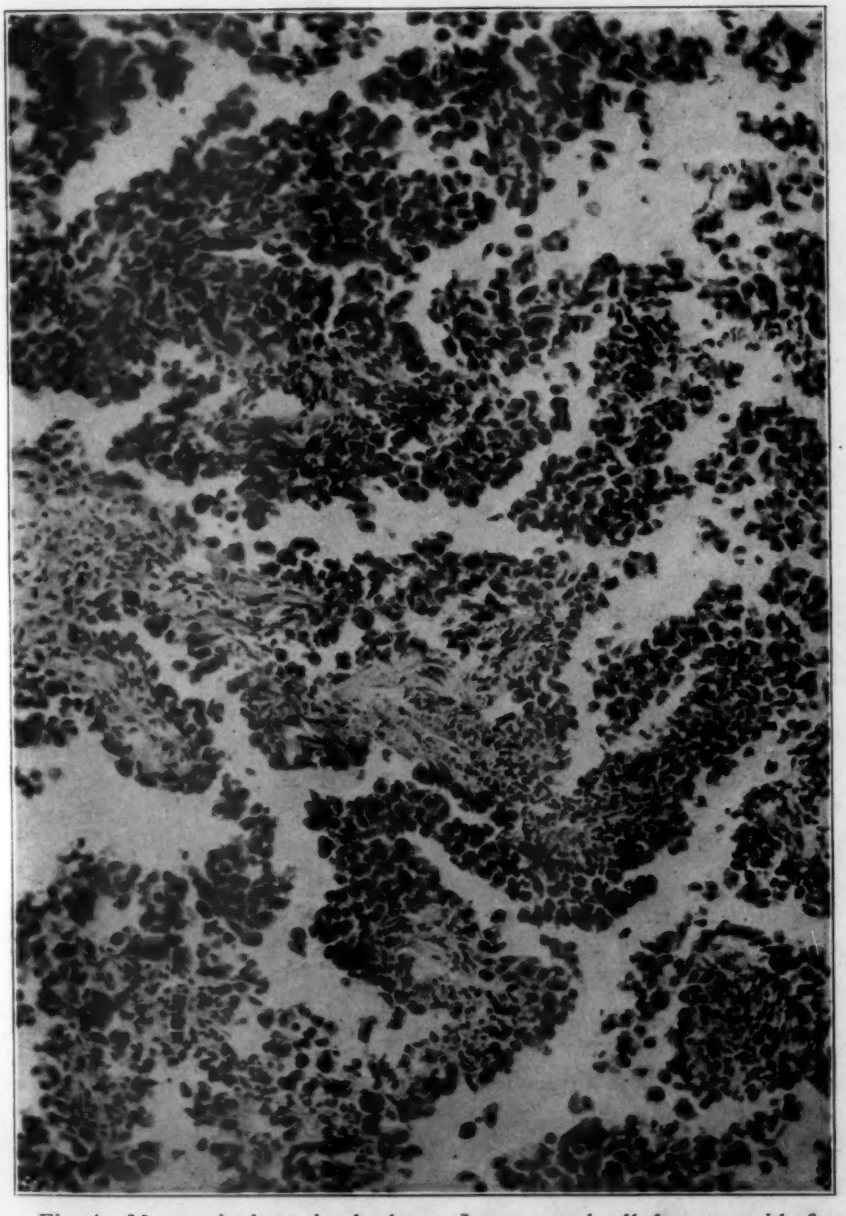

Fig. 4.—Metastatic focus in the lung. Large round-celled tumor with fine lymphoid stroma and with tongue of loose connective tissue seminoma, or embryonal carcinoma.

are reproduced in the accompanying figures. From these, it was at once evident that the original focus in the testicle, said to be embryonal adenocarcinoma, had given rise to a variety of deposits in which all three primal germ layers were represented. In figure 1 mesodermal elements in the form of an island of cartilage are the most prominent feature. In figure 2, entoderm and mesoderm are represented respectively by a cyst lined by columnar epithelium and a diffuse lymphoid stroma. Figure 3 pictures the ectodermal derivative, the interesting chorioma[9] identified by its multinucleated buds of synctium and its large glycogen-bearing cells of Langhans. Figure 4 is of particular interest and significance for the purposes of the present discussion.

Here may be seen the typical large round cells with large vesicular nuclei. In some areas, the cells are diffusely scattered in solid cords through which runs a faint lymphoid stroma; in others, a more pronounced connective tissue framework appears to form a support for indistinct alveoli. Comparison of this picture with that described and figured as characteristic of the seminome type of tumor (Chevessau,[3] Schultz and Eisendrath[4]) shows that they are identical.

COMMENT

To recapitulate, for purposes of interpretation, the case here reported presents clinically the classic sequence of events, i. e., testicular tumor, visceral metastases and death.

Although the entodermal derivative predominates in the primary tumor in the form of embryonal adenocarcinoma, the potentialities of the other suppressed layers are evidenced by a variety of visceral metastases in which all three germ layers are represented. One of these metastatic deposits discloses a structure which has been identified by advocates of Chevessau's theory as characteristic of the seminome tumor which, because of its cell morphology and its supposed homologous nature, is said to be derived from the adult cells of the seminiferous tubules, thus precluding any teratogenous relationship.

Granted the assumption that figure 4 represents characteristic seminomatous structure, it is evident that this type of tissue appears in a deposit associated with a group of tridermal visceral metastases whose origin is unquestioned. Therefore, if it is true, as stated by Schultz and Eisendrath,[4] that "in any given tumor all the metastases will be formed by the particular tissue components of the primary tumor which has taken on malignant proliferation," it follows logically that at least in this instance seminomatous tissue was a constituent of a mixed heterologous tumor of undoubted embryonal type.

If the foregoing premise is correct, one may predicate thereupon the conclusion that, at least in an isolated case, seminomatous tissue has been

9. Cooke: Chorioepithelioma of the Testicle, Bull. Johns Hopkins Hosp. **26**:215, 1915. Frank: Chorioepitheliomatus Proliferation in Teratomata, J. A. M. A. **46**:248 (Jan. 27) 1906.

demonstrated as an element of an heterologous embryonal structure of teratomatous nature.

The general conclusion seems justified, therefore, that (1) the large-celled tumor of the testicle is of embryonal type, (2) that the theory of its invariable unicellular or homologous nature is herein disproved and (3) that the evidence adduced from this case substantiates Ewing's theory of its teratomatous origin.

BONE IN ARTERIOSCLEROTIC EXTREMITIES*

SYDNEY M. CONE, M.D.
BALTIMORE

In former articles I have stated that bone is modified by circulatory alterations. The changes are progressive, retrogressive or a combination of both, depending on the predominance of passive or active hyperemia. Alternations of active and passive congestion are more influential in upbuilding than the steady continuation of either. I [1] have seen a similar pathologic condition of the ribs in more than 200 cardiovascular cases (fig. 1) of long standing. The changes in bone cells and the modification of matrix and marrow were similar to those in the cases I describe here.

Edema, softening of the matrix and enlarging lacunae relieve the bone cell from imprisonment and pressure and allow it to recover vitality. This process is marked at the borders of cancelli, especially in the spongiosa. The activity of these cells is evident in their proliferation to masses of syncytium resembling callus. I have noted this in the proliferation of bone cells in the formation of callus in transplants of bone in muscle. Osteoblasts border old cancelli, and new bone is deposited on them or on branches as new cancelli. Congestion and leakage of red blood cells add to the pabulum. Relieving the pressure allows the cells to unfold their activity in this better medium. The reticulo-endothelial system and capillaries partake of the new stimulation to growth. This is seen in the formation of connective tissue and new vessels in the marrow.

In my cases I saw regressive and progressive tissue changes involving periosteum, bone matrix and marrow without evidence of infection. The pathologic condition must be attributed to a primary circulatory cause analogous to the modification of muscle and soft parts in the experiments of Brooks [2] and Jepson.[3] Analogous changes in the liver

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* From the Department of Pathology of the University of Maryland.

1. Cone, S. M.: Bone Pathology in Relation to General Pathology, Am. J. Orthop. Surg. **6**:607, 1908; A Case of Carcinoma Metastases in Bone from a Primary Tumor of the Prostate, Bull. Johns Hopkins Hosp., no. 86, 1898; The Pathology of Osteitis Deformans, J. Bone & Joint Surg. **4**:751, 1922; Activities of Bone Cells, J. Bone & Joint Surg. **7**:894, 1925.

2. Brooks, B.: Pathologic Changes in Muscle as a Result of Disturbance of Circulation. Experimental Study of Volkmann's Ichaemic Paralysis, Arch. Surg. **5**:188 (July) 1922, ext. J. A. M. A. **79**:681 (Aug. 19) 1922.

3. Jepson, Paul: Ischaemic Contracture, Ann. Surg. **84**:785 (Dec.) 1926.

and other organs occur in old cardiovascular cases, in which atrophy and fibrosis result.

Adami [4] refers to the formation of bone and soft parts under the influence of passive congestion. He mentions the clubbed fingers in cardiac cases referring to the osteopulmonary arthropathy of Marie.

Von Recklinghausen [5] cites many cases of osteoplasia due to vascular congestion. He compares the hyperplasia of bone in chronic osteitis to elephantiasis due to congestion. He reports a case of exophthalmic goiter with vasomotor involvement and hypertrophy of the bone. He finds vital absorption and hypertrophy in congestion near metastases of cancer and reports overgrowth of bone associated with the venous congestion of varicose veins. Spencer,[6] Axhausen,[7] Stilling [8] and Greig [9] have likewise noted this association.

Greig states:

> It is possible that the circulatory disturbances which caused the varicose veins from the calf to the groin might at the same time have altered the nutritional conditions in the bone itself and so affected the vitality of the osteoblasts, altering their function.

Fehr,[10] with Greig and von Recklinghausen, notes the absorption of bone and widened lacunae due to the action of fluids of the blood in hyperemia. He refers to the enlargement and growth of the bone cells in these cases. He quotes Heitzmann (Stricker's "Jahrbücher," 1873), who stated that the changes in blood volume are held in bounds by dense cortical bone, and that a solution is necessary if the volume changes.

Ziegler [11] writes:

> In case the growing properties of the bone cell are not destroyed, the strength of the blood supply may cause new growth of bone. It is possible that the

4. Adami, J. G., and Nichols, A. G.: The Principles of Pathology, Philadelphia and New York, Lea & Febiger, 1909, vol. 2, p. 1018.

5. Von Recklinghausen: Die Fibrose oder deformierende Ostitis, die Osteomalacie und die osteoplastiche Carcinose in ihren gegenseitigen Beziehungen, Festschrift zu Rudolf Virchow, 1891.

6. Spencer, W. G.: The General Pathology of Bone, Lancet **1**:1471, 1896.

7. Axhausen, G.: Histologische Studien über die Ursachen und den Ablauf des Knochenumbus in osteoplastischen Karzinom, Virchows Arch. f. path. Anat. **195**:358, 1909.

8. Stilling, H.: Ueber Osteitis Deformans, Virchows Arch. f. path. Anat. **119**:542, 1890.

9. Greig, David M.: Osteitis Fibrosa, Edinburgh M. J. **24**:324 (May) 1920.

10. Fehr, M.: Studien über den Bank des Knochen und seines Lebeh im gesunden und kranken zustande, Arch. f. klin. Chir. **17**:19 and 232, 1874.

11. Ziegler, E.: Ueber proliferation Metaplasie und Resorption der Knochengewebe, Virchows Arch. f. path. Anat. **73**:355, 1878, Lehrbuch der speziellen Pathologie, Jena, 1906.

dissolving of bone salts starts the bone cell activity. Qualitative as well as quantitative modifications of the circulation are necessary for bone changes.

He quotes Cohnheim, who stated that the strength of the blood current influences activity of bone cells in metaplasia.

Wells [12] says:

The amount of blood supply is the important factor in determining pathological ossification. With too free a circulation there is no calcification and no ossification with too little circulation. Necrosis is followed by slow calcification and either late or no ossification.

W. G. Spencer,[6] in the Erasmus Wilson Lectures, fully describes the effects on metaplasia of bone of excessive active hyperemia, which causes absorption, and of passive hyperemia which causes hyperplasia of the bone. He considers that the growth of new bone in osteitis deformans (Paget's disease) is due to venous congestion and to hypertrophy in cardiac and pulmonary conditions. He states that mechanical influences are altered in the change of blood supply and have their part in the modification of bone.

MacEwen [13] emphasizes the mechanical influence in his work on bone, in which he shows conclusively the activity of the bone cell in the growth of new bone; relief from pressure encourages the activity of the osteogenic cell (osteoblast) and the hyperemia beyond the area of infection, causing the bone cells to become embryonic osteoblasts and to form new bone.

Todd [14] says the pressure even of soft tissues easily affects the regeneration of bone.

Bier,[15] in his extensive work on "Hyperämie als Heilmittel," accents active hyperemia as a part of functional activity and passive hyperemia as a relief to injuries and as a builder of new tissues. He also refers to the physical (mechanical) difference between active and passive hyperemia and to the longer contact of the venous blood in contact with tissues "where it can better unfold its activities."

Koenig [16] writes, "Bone grows at the point of relief from pressure and atrophies at points of greater pressure." Elting,[17] writing of osteitis deformans, says that venous dilatation may be an etiologic factor.

12. Wells, H. G.: Calcification and Ossification, Arch. Int. Med. **7**:721, 1911.

13. MacEwen, W.: Growth of Bone, Glasgow, James Maclehose & Sons, 1912.

14. Todd, T. Wingate: The Rôle of Cancellous Tissue in Healing Bone, Ann. Surg. **72**:453, 1920; abst. Am. J. Orthop. Surg. **3**:345, 1921.

15. Bier, August: Hyperrämie als Heilmittel, ed. 6, Leipzig, F. C. W. Fogel, 1907.

16. Koenig: Lehrbuch der Speziellen Chirurgie, Berlin, August Hirschwald, 1900, p. 778.

17. Elting, A. W.: Osteitis Deformans with Report of a Case, Bull. Johns Hopkins Hosp. no. 128, 1901, p. 343.

Leriche and Policard [18] believe that many diseases characterized by osseous new formations are dependent on absorption of bone caused primarily by circulatory disturbances. This in turn is due to a vasomotor phenomenon.

Heyman,[19] writing of "Osteoporosis Relieved by Sympathectomy," reports a case which suggests that the circulation is a factor in atrophy of bone. Sympathectomy relieves spasm of the foot and osteoporosis.

Fig. 1.—Cardiovascular case; bone cells proliferating in metaplastic spongiosa.

Marinesco, Putnam,[20] Dercum,[21] Spiller, Lancereaux and White [22] have explained osteitis deformans and other lesions in bone as a neurotrophic disturbance acting through vascular means.

18. Leriche, R., and Policard, A.: Some Fundamental Principles in the Pathology of Bone, Surg. Gynec. Obst. **43**:308, 1926.

19. Heyman, C. H.: Osteoporosis Relieved by Sympathectomy, J. A. M. A. **82**:1333 (April 26) 1924.

20. Putnam, James J.: Hyperostosis Cranii, Am. J. M. Sc. **112**: July, 1896.

21. Dercum, F. X., and Spiller, W. G.: Bone Syringomyelia, Am. J. M. Sc. **112**:672, 1896.

22. White, E. P. C.: Osteitis Deformans in Monkeys, Arch. Int. Med. **30**:790 (Dec.) 1922; Osteomalacia, Arch. Int. Med. **30**:620 (Nov.) 1922.

Krogh's [23] work leads one to relate the nerves, vessels and endocrine glands in a composite effect on pathologic conditions of bone. "Capillary tone is maintained by the sympathetics which keep them tonically contracted through the stimulus of a substance normally present in the blood." Krogh thinks the pituitary hormone in minute quantities has this effect.

Fig. 2.—Arteriosclerotic gangrenous toe, showing new-formed cancelli, fibrous marrow, plasma cells and arteriosclerotic vessels.

White [22] states that a larger calcium diet starts a neurotrophic upset, which causes perversion of the ductless glands, hyperemia and absorption of calcium.

23. Krogh, cited in: The Capillaries in Health and in Disease, editorial, J. A. M. A. **80**:1144 (April 21) 1923.

The experiments on new formation of bone in kidneys and elsewhere indicate vascular congestion as the cause. Asami and Dock,[24] and Pearce,[25] obtained bone formation in the kidneys after tying the renal vessels.

Fig. 3.—New formation of bone projecting from the marrow as an osteophyte on a gangrenous toe.

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24. Asami, Goichi, and Dock, William: Experimental Studies on Heteroplastic Bone Formation, J. Exper. Med. **32**:745, 1920.

25. Pearce, R. M.: Later stages of the Repair of Kidney Tissue (Dog) with Special Reference to Proliferation of the Pelvic Epithelium and Heteroplastic Bone Formation, J. M. Research, **20**:53 (Jan.) 1909.

Rogers [26] reports osteitis without infection, quoting Preiser, who suggests injury to the blood supply as the cause of the pathologic conditions of bone. Speed,[27] describing the asymmetrical growth in length of long bones following osteomyelitis, mentions a case in which trauma without infection was the source of the new growth. Spencer [6] refers to the increase in growth of bone in typhoid fever, due to the greater blood supply during the fever.

Rost's [28] experiments in which he produced granulation tissue and enlargement of bone by injecting noninfectious material into bone might be similarly explained.

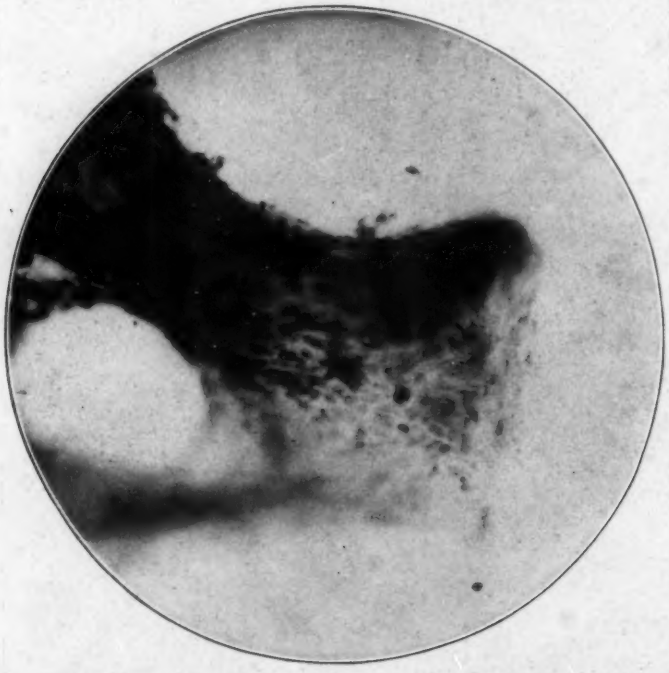

Fig. 4.—Syncytium of bone cells in congested edematous cancellus of gangrenous toe.

Johnson's [29] valuable work on the circulation in bone explains the unusual higher percentage of hyperplastic changes in the outer cortical

26. Rogers, Mark H.: Traumatic Osteitis of the Wrist, Surg. Clin. N. Amer. **1**:697 (June) 1921.

27. Speed, Kellogg: Longitudinal Overgrowth of Long Bones, Surg. Gynec. Obst. **36**:787 (June) 1923.

28. Rost: Experimentelle und klinische untersunchungen über chronische, granulierende Entzundungen des Knockenmarks, Deutsche Ztschr. f. Chir. **125**:83, 1913.

29. Johnson, R. W., Jr.: A Physiological Study of the Blood Supply of the Diaphysis, J. Bone & Joint Surg. **9**:153 (Jan.) 1927.

bone in my cases. Here there is a blood supply not only from nutrient and metaphyseal vessels, but also from the periosteal circulation.

PATHOLOGIC CONDITIONS IN THIRTY CASES OF ANTERIOSCLEROTIC TOES

In six cases of arteriosclerotic toes ulceration had occurred, but in only two instances did the infiltration of leukocytes extend to the periosteum. Pus or

Fig. 5.—Formation of cysts by coalescence of adjacent haversian canals; arteriosclerotic toe.

granulation tissue was not found in the marrow or cortex in any case. This excluded the suggestion of infection. The cartilage was softened and opaque in two cases, doubtless owing to edema. The bone was usually less hard than normal. Here edema with vital absorption must have been at work. In two instances it was unusually dense, the entire medullary cavity being filled by closely grown cancelli (fig. 2).

Arteriosclerosis, congestion, pigmentation and edema were found in all cases. The subcutaneous tissue was fibrosed in all, spindle cells and connective tissue following the large and small vessels. Masses of sclerotic connective tissue were present in most cases. Occlusion of vessels was present in varying degrees, some being entirely obliterated by fibrous tissue, others having a narrow lumen.

The periosteum was cellular in thirteen cases and demonstrated formation of new bone in twelve. New bone was seen in the marrow in eleven cases (fig. 3), deposited along old cancelli or vessels. In two cases (fig. 3) this new bone

Fig. 6.—New bone formation on old cancellus. Fibrous marrow.

followed a cleft in the cortical bone, following vessels and forming minute osteophytic growths which caused the periosteum to bulge. The bone cells were active in sixteen cases—they were enlarged and divided and were often free at the margins of the swollen (edematous) cancelli. They were often seen in rows of pentagonal cells or as syncytium bordering the cancelli (fig. 4). The haversian canals were completely or partially filled with cellular fibrous tissue in eight cases.

The lacunae were widened at the borders of cancelli in all cases. In three instances adjacent canals had coalesced, suggesting cyst formation (fig. 5). Metaplasia of bone to cellular fibrous tissue was noted in five cases. The marrow was fatty in one case and fibromyxomatous or fibrous in the others (fig. 6). Its

vessels were congested and frequently thrombosed, with walls thickened by young cellular fibrous tissue. Calcification of vessels was seen in three cases. New capillary loops were not uncommon (fig. 7); these new capillaries were lined by active endothelial growth and had well defined fibrous walls. Small round cells or polymorphonuclear leukocytes were seen in only two cases. Plasma cells were present in large numbers in two cases, osteoblasts lined cancelli in five (fig. 2); osteoclasts were present in five and minute bone spicules in four.

Fig. 7.—New capillaries in marrow of gangrenous toe.

SUMMARY

Progressive and retrogressive changes in bone and in soft parts were seen in thirty cases of gangrenous extremities. The circulation varied in each, passive hyperemia being the predominant factor. The retrogressive changes were atrophy and vital absorption of bone. The progressive and retrogressive changes varied with the vascular modifications. Metaplasia of bone and activity of bone cells occurred. The new bone formation and fibrosis of the marrow were the predominant features in these cases.

EFFECT OF PREGNANCY ON THE EMPTYING OF THE GALLBLADDER

A PRELIMINARY REPORT *

FRANK C. MANN, M.D.
AND
GEORGE M. HIGGINS, PH.D.
ROCHESTER, MINN.

Boyden's [1] observation that a meal of egg-yolk and cream caused the gallbladder of the cat to empty has formed the basis for the most important of the recent advances made in the study of the physiology of the biliary tract. Boyden's observation has been corroborated by several investigators using many species of animals. It has also been shown that the evacuation of the contents of the gallbladder is due to the contraction of its intrinsic musculature. A complete review of the recent data with regard to the emptying of the gallbladder has been presented by Whitaker.[2] The mechanism involved in causing the gallbladder to contract and the reason why fat should be so potent in this respect have not been determined; nor is the relation of the sphincteric mechanism of the common bile duct to the emptying of the gallbladder definitely established. Work on the latter problem was summarized recently by Giordano and Mann.[3]

Reasoning from the character of similar physiologic mechanisms, the origin of the stimulus causing the gallbladder to contract and to expel its contents would be considered as nervous or chemical or both. If a chemical stimulus were operative, it was thought that the part played by it could be demonstrated by feeding pregnant animals with egg-yolk and cream, and then, by removing the fetuses when the mothers' gallbladders were empty, it could be determined whether or not the fetal gallbladders had also expelled some of the contents. While there are many serious objections to this line of attack, the chief of which is the known imperviousness of the placenta to many substances, and while negative results would not be of value, if the gall-

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* From the Division of Experimental Surgery and Pathology, The Mayo Foundation.

1. Boyden, E. A.: The Effect of Natural Foods on the Distention of the Gallbladder with a Note on the Change in Pattern of the Mucosa as it Passes from Distention to Collapse, Anat. Record **33**:333, 1925.

2. Whitaker, L. R.: The Mechanism of the Gallbladder and its Relation to Cholelithiasis. J. A. M. A. **88**:1542 (May 14) 1927.

3. Giordano, A. S., and Mann, F. C.: Some Observations on the Sphincter of the Choledochus, Tr. Sect. Path. and Physiol., A. M. A., 1927, and Arch. Path. and Lab. Med. (to be published).

bladder of the fetus did empty with that of the mother it would be suggestive evidence that a chemical mechanism is responsible for the emptying.

Accordingly, a group of dogs in various stages of pregnancy was observed in the following manner: The animal was made to fast for a period of about sixteen hours, and then a standard meal of egg-yolk and cream was given. Approximately from four to four and a half hours afterward, a time at which the gallbladder of the normal dog is partially or completely empty, the animal was etherized and the biliary tract explored. We were surprised to find that the gallbladder was filled, and often distended, with thick, dark bile. Of the large series of dogs examined, only a few showed slight evidence that the gallbladder had partially emptied. The length of time between feeding and exploration was therefore gradually lengthened. A large series of dogs in different stages of pregnancy was examined at various periods after the ingestion of the standard meal of egg-yolk and cream, and in only a few, explored after a period of eight and ten hours, respectively, was there any evidence that the gallbladder had even partially emptied. In contrast with these results are the results in a large series of nonpregnant dogs in which, with few exceptions, the gallbladder was found partially or completely empty approximately four hours after the standard meal had been taken.

Since the effect of pregnancy on the emptying of the gallbladder following the standard meal was so definite in the dog, other species of animals were investigated. In the only pregnant cat near term that we were able to obtain, the gallbladder emptied completely within the usual time following the ingestion of the food. A large series of pregnant guinea-pigs was examined four hours after being fed egg-yolk and cream, and in no instance was there evidence that the gallbladder had emptied. On the other hand, there is usually evidence of its emptying in the nonpregnant guinea-pig four hours after the ingestion of the fat meal.

Further experiments were carried out on the thirteen-striped gopher (*Spermophilus citellus-tridecemlineatus*), a small rodent which abounds in this region. Within a few days after coming out of hibernation in the spring, all the females become pregnant. The period of gestation is twenty-eight days.[4] It was thus possible to obtain large numbers of pregnant animals of this species. A series of these animals was obtained which included males, nonpregnant females and females at various stages of pregnancy. It was possible to study the pregnant

4. Drips, Della: Studies on the Ovary of the Spermophile (Spermophilus Citellus Tridecemlineatus) with Special Reference to the Corpus Luteum. Am. J. Anat. **25**:117, 1919.

female of the species from the time the fetuses were only a few days old through all the stages of pregnancy to term. It was found that the gallbladders of the males and nonpregnant females of the species observed four hours after the ingestion of a meal of egg-yolk and cream, were always completely empty. The gallbladder of this species emptied as completely as that of any species we observed. The degree of emptying in the pregnant female, however, depended on the stage of pregnancy. In animals observed in the early stages of pregnancy, slight emptying had occurred four hours after the taking of the "fat" meal, although in no instance, even in early pregnancy, was the degree of emptying comparable with that of the nonpregnant animal. From about the time of the middle of pregnancy to term, there was no evidence of the emptying of the gallbladder (figs. 1 and 2).

Fig. 1.—Livers of pregnant female (left) and male gophers, four hours after feeding egg-yolk and cream. In the female the gallbladder is completely distended, while in the male it is empty.

The effect of the pregnant condition in preventing the gallbladder from emptying is demonstrated definitely in the following experiments: Pregnant dogs were given the fat meal and explored at various periods afterward. The gallbladder was distended with dark bile. The fetuses were removed, and two or three days later the animals were again fed and explored. At this time the gallbladder had emptied in the same manner and to the same extent as in the normal dog. The gallbladders of gophers which had given birth to young two days previously emptied completely after their fat food. The gallbladders emptied partially in two dogs in which the fetuses were found dead on exploratory operation.

Comparison of the gallbladders of a pregnant and nonpregnant animal four hours after a meal of egg-yolk and cream demonstrates in a striking manner the difference in the response of the biliary mechanism

to the food. The gallbladder of the nonpregnant animal is partially or completely empty. It is flaccid, and the surface is pale. In the dog, a species in which the capsule of Glisson is reflected over and firmly attached to the gallbladder, the reflected edge of the capsule, which is hidden when the gallbladder is full, can be readily seen. If the remaining content is withdrawn, it is often much lighter in color than normal because of the entrance of bile directly from the liver in the process of refilling the gallbladder. The gallbladder of the pregnant animal, on the other hand, is different. It is full and often distended four hours after the fat meal has been taken. It is dark, and the bile is dark and so thick that it is withdrawn by a syringe

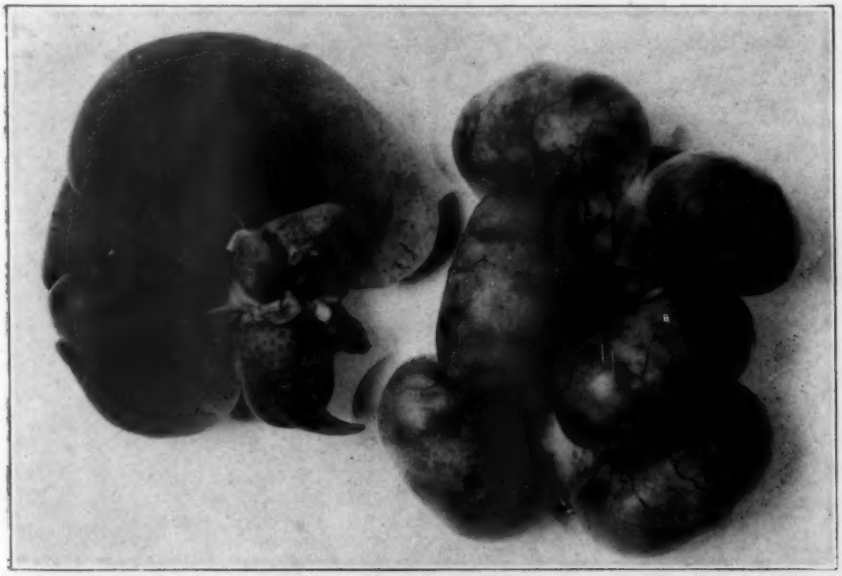

Fig. 2.—Liver and fetuses of female gopher, four hours after feeding egg-yolk and cream. The gallbladder showed no evidence of having emptied.

with difficulty. The bilirubin content of such bile, as measured in van den Bergh units, is usually a high normal (fig. 3). Forty per cent iodized oil injected into the gallbladder of a pregnant dog may not be subsequently expelled following a fat meal but remains for weeks, slowly diminishing in amount.

A comparison of two gallbladders, one of a nonpregnant animal, which emptied, and the other of a pregnant animal, which did not empty, raises questions with regard to the so-called tests of function of the gallbladder. The gallbladder of the nonpregnant animal appeared normal grossly, and emptied and filled normally. The gallbladder of the pregnant animal appeared normal grossly but did not empty normally.

Its contents showed the characteristics of stasis. Also, shortly after removal of the contents of the uterus, the gallbladder of the pregnant animal again responds normally in every respect. It is apparent that activity of the gallbladder may be influenced by factors outside the biliary tract and that the organ should neither be judged diseased or be removed because of its response to these extraneous factors, which may be physiologic.

It is obvious that in order to determine the reason why the gallbladder of the pregnant animal usually does not empty following the ingestion of the fat meal, one must know more concerning the normal mechanism of emptying.

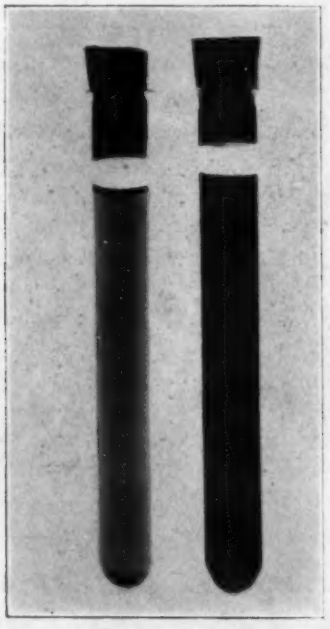

Fig. 3.—Samples of gallbladder bile taken from a nonpregnant female (left) and pregnant female four hours after feeding egg-yolk and cream. The bilirubin content of the gallbladder bile of the nonpregnant dog was 5 units (van den Bergh), while that of the pregnant female was 58 units.

In considering the cause preventing the gallbladder of the pregnant animal from emptying, the changes in the size of the abdominal cavity and in intra-abdominal pressure associated with the growth of the fetuses should be considered, not only because they are the most prominent changes occurring during pregnancy, but also because certain investigators still believe that changes in intra-abdominal pressure are important factors in causing the gallbladder to empty. There are two facts which suggest that the increase in pressure within the abdomen is a factor in preventing the gallbladder from emptying: the

relation of the degree of emptying to the stage of pregnancy, particularly as noted in the gopher, and the complete emptying a short time after the fetuses have been removed. However, certain observations are not in accord with the view that the increase in intra-abdominal pressure due to the growth of the fetuses is of primary importance in the failure of the gallbladder to empty. While there was some evidence of the emptying of the gallbladder early in pregnancy, failure of the emptying process to proceed normally has been observed at a time when the fetuses were too small to affect the pressure conditions within the abdomen to any degree. The variation in the size of the abdomen, associated with the ingestion of food and the expulsion of fecal material is greater in early pregnancy in the guinea-pig in which the gallbladder does not empty than in the nonpregnant guinea-pig in which the gallbladder empties completely. Furthermore, in two dogs in which the

Fig. 4.—Liver and fetuses of gopher four hours after feeding egg-yolk and cream; contrasted with liver of gopher which had carried paraffin balls, equal in displacement to late fetuses, in the peritoneal cavity for three weeks before it was given the standard meal of egg-yolk and cream. Note differences in size of the gallbladders of the two animals.

fetuses were found dead at exploratory operation, the gallbladder had partially emptied. It was also noted that the pregnant cat whose gallbladder emptied completely had a greatly distended abdomen.

Definite evidence to show that the increase in the abdominal content was not an essential factor in preventing the gallbladder of the pregnant animal from emptying was obtained by artificially increasing the contents of the adbominal cavity and then administering the standard meal. This was done as follows: Balls of paraffin (melting point 43 C.) of the approximate size of the fetuses of the gopher late in pregnancy were made and sterilized in alcohol. Male and nonpregnant gophers were etherized, and through a small opening in the abdominal cavity, the paraffin balls were inserted in sufficient quantity to approximate the degree of abdominal distention in the pregnant animal in which

the gallbladder had failed to empty. A more accurate means of comparison was the determination of the amount of paraffin to be inserted from the amount of water displaced by the fetuses. Several days were allowed to elapse between the placing of the paraffin in the abdominal cavity and the feeding of the fat meal. When the animal had appeared normal for several days, the usual amount of egg-yolk and cream was given, and the animal was killed at the end of four hours. It was found that the gallbladder had emptied completely (fig. 4).

A more important consideration bearing on the emptying of the gallbladder of the pregnant animal has to do with the mechanics of the gastro-intestinal tract. Those who have studied the emptying of the gallbladder following the fat meal are agreed that the viscus empties best when the absorption of the fat has been rapid. When the fat leaves the stomach and is absorbed from the intestine at a rate which distends the lacteals and colors the mesenteric lymph nodes white, the gallbladder is usually found to be empty; whenever the lacteals are faintly delineated, only partial emptying, if any, will take place. In the pregnant animal the fat appears to leave the stomach more slowly than normally, and the lacteals are usually only faintly delineated and not distended. The entire mechanism of the gastro-intestinal tract appears to have slowed down, and the degree of slowing is such that the emptying of the gallbladder either does not occur or is greatly delayed and incomplete.

SUMMARY

Our observations show that the gallbladder of the pregnant dog, guinea-pig and gopher usually does not empty following a feeding of egg-yolk and cream, while in the nonpregnant animal it usually partially or completely empties. Partial emptying has been noted in early stages of pregnancy, and in a few dogs it has been noted late in pregnancy. However, in no instance [5] in the large number of animals observed did the gallbladder of a pregnant animal of these three species empty in the time and to the degree that it emptied in the nonpregnant animal. The gallbladder of one pregnant cat emptied in the same manner as that of a nonpregnant cat. A large number of pregnant cats and pregnant animals of other species must be examined before it can be accepted as a general physiologic fact that the gallbladder of the pregnant animal does not empty in a similar manner following the ingestion of the standard fat meal as it does in the nonpregnant animal. However, sufficient data have been secured in regard to three species to make it appear probable that similar observations will be made with other species, including man.

The results of these experiments cannot be applied to the human being without qualification until it has been determined that the gallbladder of the pregnant woman does not empty in the normal manner

following the feeding of fat. However, three considerations are pertinent to the subject. The pathologic conditions often associated with pregnancy which may directly or indirectly have some relation to the mechanism of the biliary tract are: (1) hyperemesis, (2) eclampsia, and (3) gallstones. Further observations with particular reference to the normal mechanism of the biliary tract must be made before definite conclusions can be reached.

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5. Since this article was written a few pregnant dogs have been observed in which the gallbladder emptied.

REDUNDANT COLON *

HARRY GAUSS, M.D.
DENVER

The redundant colon is one that is too long for its owner. Kantor [1] considers it a form of congenital anomaly compatible with life and health under reasonably favorable circumstances, which under unfavorable stress and strain of life may give rise to a symptom complex of annoying and distressing manifestations. Some persons with redundant colon may never develop symptoms referable to it; others may have trouble all the time; many may be symptom-free for many years and then develop a clinical syndrome.

The whole conception of the normal anatomy of the colon, and with it the concept of the redundant colon, is undergoing a rapid transition at present. This revision is a logical supplementary study to the changed notions of the normal variations of the stomach compared to the prevailing acceptance of the so-called normal type of stomach only fifteen years ago, when the current teaching was that the normal stomach was a fundus-shaped pouch lying under the arch of the left side of the diaphragm. Today the older notions of a single stereotyped kind of stomach have been displaced by the idea that there are a series of normal types varying from the fishhook to the steerhorn type, with several intermediate types. Correspondingly, the variations of the normal colon are being studied anew, although a standard type of colon has been accepted for many centuries; ultimately, a classificaion will be made. At present I cannot say whether the redundant colon is a variation of the normal type, or as Kantor believes, a mild form of congenital anomaly. Certainly, at times it gives rise to a symptom complex, which easily may be recognized with the aid of the roentgenogram and which demands medical attention. The symptom complex in itself does not make it a congenital anomaly. Variations in the shape of the stomach with the accompanying inherent physiologic attributes also give rise to symptom complexes at times, yet fall within the limits of the so-called normal type of stomach. The actual length of the colon is of secondary importance; the significant feature of the redundant colon is that it is too long for the person who possesses it, so that it falls into loops and kinks which create mechanical interference with the free movements of the colonic contents. The great variation

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* From the Department of Medicine, University of Colorado School of Medicine.

1. Kantor, J. L.: Am. J. Roentgenol. **12**:414, 1924.

in the length of the colon is brought out in the observations of Bryant [2] on the colons of 160 adults. He found that the colon varied in length from 3 feet and 4 inches (101.6 cm.) to 10 feet and 10 inches (330.2 cm.), with an average of 5 feet and 2 inches (157.5 cm.); studying the ratio of the length of the colon to the small intestine and the length of the colon to the length of the body, he observed that in the adult the ratio of the length of the body to that of the small intestine is about 1 : 3.7; the ratio of the length of the colon to that of the small intestine is about 1 : 4; that the colon of the adult about equals the length of the body, and that the small intestine is about four times the length of the body.

Davis [3] studied the colons of 285 persons coming to postmortem examination for the purpose of determining the relative position of the segments of the colon, the nature of the usual angulations and the extent of deviated morphology consistent with physiologic function. He found that only 32.5 per cent of the colons conformed to the stereotyped description often seen in textbooks, even when due allowance was made for the agonal and postmortem changes; he did not consider these influences of great importance in the final conclusions. In 55 per cent of his series, he observed convincing evidences of etiologic conditions for constipation. He observed distinct enlargement of the colons proximal to the constricted splenic flexure in 8.4 per cent of the cases; in 4.3 per cent the pelvic colons did not show angulation, only a slight curving being evident from the midportion of the descending colon to the segment of the rectal tube; in 1.2 per cent the ceca were fishtail in shape and in 20.7 per cent decidedly pouched in form; the ascending colon was found in an oblique position in 13.7 per cent, and in 0.6 per cent it was in a horizontal position; the transverse colon was found markedly ptosed in 23.4 per cent; the splenic flexure was absent in 4.2 per cent, coiled in 1.2 per cent and the form of a clothes pin in 2.1 per cent. The descending colon was found to be coiled between the splenic flexure and the pelvic brim in 4.2 per cent; the pelvic colon was almost straight in 16.8 per cent and acutely angulated in 16 per cent, coiled in 3.1 per cent and appeared over on the right side in 2.4 per cent. He concluded that exceptions were so frequent that the colon cannot be considered to conform to any present descriptive morphography.

From the studies of Davis and other investigators, it is rapidly becoming evident that the description of the colon that has been used for many centuries must give way to a newer, broader description. Descriptions of the colon observed at laparotomy are helpful, but more than a single portion of the colon is rarely seen at operation; and when

2. Bryant, John: Am. J. M. Sc. **167**:499, 1924.
3. Davis, J. E.: Am. J. Obst. **73**:474, 1926.

symptoms arising from the colon demand surgical intervention, they usually indicate an extreme type of lesion. The minor variations, the common lesions comprising the bulk of the diversified anatomic forms of the colon, do not demand or even invite surgical intervention, and

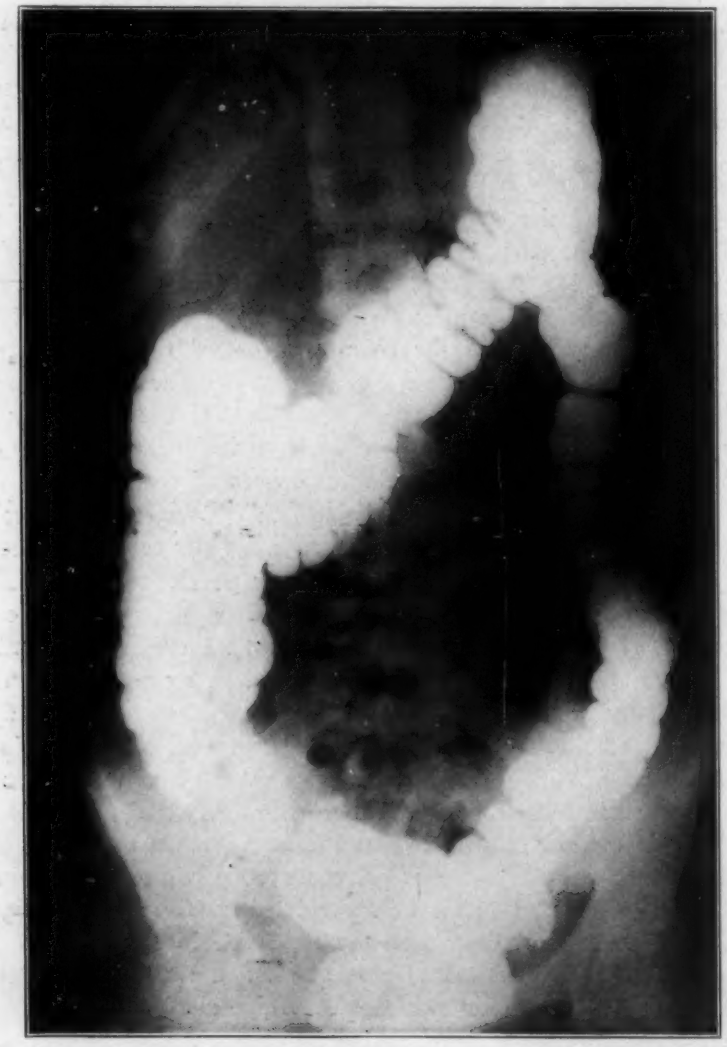

Fig. 1.—Approximately normal colon in a young woman.

knowledge of them must come from postmortem examinations and roentgen-ray studies conducted on an appreciable number of persons.

My purpose in this paper is to emphasize the identity and symptomatology of redundant colon and to report some cases illustrating its characteristics.

The redundant colon is one that is too long for the person who possesses it. It is characterized by its increased length, which causes loops, kinks or deviations from the normal colonic pathway, which interfere with the free movements of the colonic content and give rise

Fig. 2.—Approximately normal colon in a young man.

to clinical symptoms. The redundancy may be general or local. The entire colon may be too long and too loose, or a segment may be too long, thereby creating a kink, loop or double loop. According to White, two thirds of the loops are found on the left side of the colon in the sigmoid, descending colon or splenic flexure.

PATHOGENESIS

The colon is essentially an excretory organ. Its function is the formation of feces and the elimination of them from the body. Although the colon is in continuity with the small intestine, it has few physiologic properties in common with it. The small intestine is essentially an organ of digestion and absorption. The word "small intestine" is associated with "food," the word "colon" is associated with "feces." The peristalic wave that can be so readily observed in the small intestine is rarely observed in the colon. Only a few observers can boast of ever having seen colonic movement in human beings—Hurst [4] mentions his own experiments and also that of Holzknecht and Case—whereas the peristalsis of the small intestine is an observation made by almost every one who has looked through a fluoroscope. The digestion of food takes place largely in the small intestine, and is considered completed when the intestinal chyme has passed through the ileocecal valve. Ferments to assist in the digestion of food are produced in the mucosa of the small intestine; there is no evidence of the formation of ferments in the large intestine. Absorption, which takes place largely in the small intestine, takes place sparingly in the colon. The subject of colonic absorption has been widely discussed and has finally resulted in a complete revision in the uses of the nutrient enema which was at one time a favorite therapeutic agent. Enemas of egg and milk, together with many other so-called nutrient enemas, have been discarded, since it has been shown that absorption in the colon is limited to water, salt, sugar and simple amino-acids. It is the last named factor, namely, the ability of the colon to absorb simple amino-acids, which is at the basis of much of the distressing symptomatology of redundant colon. Further, whereas the small intestine has an almost liquid medium to propel, the colon has a more solid, putty-like content which demands a more vigorous muscular tone. The passage of colonic contents depends largely on the contractility of the three longitudinal muscular bands. Should these longitudinal fibers become atonic, the bowel loses tone. In many patients the initial reaction is to employ cathartics and enemas or to strain at stool, but these abuses only preface a pathologic redundancy. The chemical reaction of the colonic contents is slightly alkaline. Should the alkalinity increase, the fecal mass becomes a favorable medium for the propagation of putrefactive toxicogenic organisms. Within certain limits no harm results, providing the feces are periodically expelled, but with loss of muscular tone and resulting colonic stasis, absorption of the end-products of this bacterial activity is favored. The bacteria split up the higher protein molecules into many intermediate substances, including amino-

4. Hurst, A. F.: Constipation and Allied Intestinal Disorders, London, Oxford University Press, 1921.

acids and their derivatives, such as indol, skatol and phenol. If the decomposition proceeds further, other highly toxic substances are developed, such as putrescine, cadaverine and others; the absorption of these can produce a severe clinical reaction and may account for the toxic symptoms of chronic constipation. This view is by no means universally accepted. Among the skeptics is Hawk,[5] who questions the specificity of the latter substances as the direct etiologic factor in disease. However, it must be borne in mind that the specific proof is a tremendously laborous chemical problem. Novello, Wolf and Sherwin[6] apparently studied 13,000 pages of the literature dealing with the chemical side of intestinal putrefaction without solving the full problem of abnormal disintegration of amino-acid; but they succeeded in showing experimentally that as small a dose as 0.1 mg. of indol and skatol, which are products of disintegration of the amino-acid tryptophan, when taken into the intestine in capsules covered with salicin caused a distinct feeling of nausea followed by loss of appetite, belching and a dull headache which persisted for at least twelve hours. Even Hawk admits that the absorption of these substances is probably the chief factor in producing "bowel breath," nausea and headache in the pathogenesis of constipation. Although Novello, Wolf and Sherwin observed that phenol taken in 1 per cent solution produced no untoward effects, the corrosive action of this substance is too well known to consider the subject closed. Its local action from prolonged absorption in colonic stasis is yet to be explained.

As long as the redundant colon functions properly, it does not cause distressing symptoms; but when it becomes overfilled, twisted or packed, it tends to obstruct the normal movement of the colonic contents, which results in stasis and increased putrefaction, and gives rise to a whole train of symptoms, such as headache, gas distress, physical and mental fatigue, irritability, sleeplessness and other symptoms. The gases liberated in the colon also merit consideration and play a significant rôle in the causation of the symptoms of redundant colon. Gas distress is second only to constipation in the frequency of the symptomatology of redundant colon. Commonly it is mild but annoying; at other times it may cause acute abdominal pain as a result of increased intravisceral tension. Much of the distress from intestinal gas may be traced directly to the mechanism of the redundant colon. In the normal process of digestion, certain gases, such as carbon dioxide, hydrogen, nitrogen and methane, and to a lesser extent, hydrogen sulphide, are liberted as the end-products of digestion. The absorbable gases, such as carbon dioxide, and to a lesser extent, methane, are absorbed into the circulation and excreted through the respired air; while the less absorbable gases, such as nitro-

5. Hawk, P. B., and Bergheim, O.: Physiological Chemistry, Philadelphia, P. Blakiston's Son & Company, 1926.

6. Novello, N. J.; Wolf, W., Sherwin, C. P.: Am. J. M. Sc. **152**:888, 1925.

gen, hydrogen, and hydrogen sulphide, are passed through the rectum. About 1 liter of gas is passed through the rectum daily, while larger amounts are absorbed into the blood stream and so eliminated from the intestinal tract. In normal metabolism, a person suffers little from the passage of gases, but when the formation of gas is excessive or its passage is obstructed, the patient experiences abdominal consciousness then later, distress. Redundant colon may interfere with the elimination of gas in three ways: 1. By its loops, kinks, or folds, the redundant colon distorts the normal pathway for the colonic contents and may constrict the lumen of the intestine. 2. The redundant colon is a common cause of constipation, and the retained fecal masses by obstruction may decrease the lumen of the intestine. 3. By its liability to impair the circulation within the blood vessels which supply the loop by reason of pressure, torsion or traction, it may diminish the rate of absorption of the gases within the colon. The last view is supported by the experiments of Gatch, Trusler and Ayers,[7] who have shown by experiments on animals that when the pressure of gas within an occluded loop is increased, there is a proportionate decrease in the rate of blood flow through it, which may lead to anemic stasis of the blood in that part of the intestine; gaseous distention alone may result in severe pathologic reaction, including necrosis.

Redundant colon causes constipation by altering the normal pathways of the colon or by constricting its lumen. In constipation there is an interplay of spasticity and atony with a predominance of the former. This pathologic function is also operative in redundant colon, except that in simple constipation it involves the entire colon; in redundant colon, this interplay of muscular tone may be limited to the site of the redundancy. The redundancy is not a fixed barrier to the movement of the colonic contents; it tends to become so only when it is overfilled, overdistended or kinked, when it gives rise to symptoms. When its pathway is cleared and it is functioning properly, the symptoms subside. The pathologic condition of redundant colon is that of a functional disorder superimposed on an organic condition. Neither condition is sufficient to cause its symptomatology, and the acceptance of this basis for the pathologic condition assists one in understanding the observation that this condition, which is latent since birth, may cause symptoms in the adult.

INCIDENCE

In a review of 1,000 consecutive cases of gastro-intestinal disease in private patients, White [8] reports forty-three in which there were varying

7. Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Effects of Gaseous Distention on Obstructed Bowel; Incarceration of Intestine by Gas Traps, Arch. Surg. **14**:1215 (June) 1927.

8. White, F. W.: M. Clin. N. Amer. **8**:1611 (March) 1925.

degrees of redundancy. In a similar series of 668 cases, Kantor [1] reports 9.2 per cent in which there were redundant colons. Bryant's [2] observation that there were elongated (redundant) colons in 15 per cent of his cases studied at postmortem is probably a more accurate figure, as many persons possessing the condition probably escape clinical observation. Regarding the incidence of redundant colon among the sexes, both Kantor and White report the greater frequency, about 60 per cent, in males, in spite of the many observations by surgeons of visceroptosis in the laparotomized sex. With reference to the relationship of the redundant colon to the body habitus, the reports of both Kantor and White are even more surprising. They found redundant colons in only 30 per cent of the asthenic type of persons; the remainder occurred either in the sthenic (stocky) or intermediate types.

SYMPTOMS

Some persons with redundant colon may never have symptoms; some may have symptoms occasionally, and others may have them all the time. All of the patients have an underlying predisposition to malfunction of the colon. Among the contributory causes are the stress and strain of life, wasting disease, operations, pregnancy, improperly balanced diet, insufficient exercise, bad hygiene, habit of using cathartics, worry and mental depression. Constipation is the commonest symptom. Usually it is of many years' duration, and frequently the patients are habitual users of laxatives and enemas. Gas distress is the symptom of next greatest frequency. It may be manifest as flatulence, increased gas movements or increased flatus; as abdominal distention resulting from inability to move the gas; or as belching, when the belching is unproductive of considerable relief, since it represents a futile attempt of the patient to rid himself of gas in the splenic flexure. Occasionally, accumulation of gas in the splenic flexure may cause precordial distress and palpitation as a result of pressure under the diaphragm.

Pain in the abdomen is the next symptom of importance. This varies in degree from mild discomfort to violent colic. The pain may be general or localized. Localized pain usually corresponds to the site of the redundant colon. It is probable that it is the pain of redundant colon which leads to errors in its diagnosis, and patients are frequently operated on for appendicitis. In the series of cases of Kantor and White, and in my series, are instances in which the patient had been operated on for appendicitis and the symptoms had persisted after operation; later the patient responded to treatment for redundant colon. The pain may be associated with gas distress resulting from increased intravisceral tension. Vomiting occurs occasionally but is not characteristic. Diarrhea, another occasional symptom, probably results from a

mild colitis, which is caused by an irritation of the intestinal mucosa resulting from colonic stasis or by the use of vicious cathartics or enemas.

DIAGNOSIS

The diagnosis is suggested by the history of colonic malfunction and confirmed by the roentgenogram showing the redundant loop. A history of constipation of long duration is suggestive, especially if it dates back to childhood; also a history of prolonged periods between stools and occasional enormous evacuations. Gas distress points to redundant colon, especially if it is persistent and occurs in young adults, and does not respond to the treatment for simple intestinal putrefaction or fermentation. The positive diagnosis can be made only by roentgen-ray examination. Both the opaque meal and the barium enema method are employed. The loop, or kink, is usually visualized best by the enema study, but its mechanism for obstruction is followed better by a study of the opaque meal. The redundant colon possesses the characteristics of a dual entity, an organic structure which under certain conditions of strain gives rise to a function disorder, and the symptoms are largely the result of its functional rather than of its organic nature. The symptoms result from the interplay of colonic spasm and atony, the constipation, the increased intravisceral pressure resulting from gas distress, and other symptoms. When these symptoms involve the greater part of the colon, they usually suggest a condition of colonic malfunction, and a study of the roentgenogram clears up the diagnosis; but when these symptoms involve only the redundant loop, they are apt to remain local and thus give rise to a confusion with disturbances of the organs in juxtaposition with the loop, the roentgen-ray examination may be omitted, and an error in diagnosis is likely to occur. Kantor reports the case of a physician, aged 45, who was constipated all his life and who used cathartics habitually; his condition had been diagnosed as duodenal ulcer; later, he had had his appendix removed because of atypical recurrent abdominal pain; finally, his condition was diagnosed as redundant colon, which was confirmed by roentgen-ray examination. Patients W. J. D. and M. A. N. of my series are almost similar and also occur in physicians. Redundant colon must be differentiated from appendicitis—especially the so-called chronic and atypical appendicitis—from duodenal and gastric ulcer, cholecystitis, cholelithiasis and carcinoma of the colon. The fact that six of my series of eleven patients had had their appendixes removed is worthy of consideration. The differential diagnosis is made by employing every available diagnostic procedure—clinical, laboratory and roentgen ray. Of course, two conditions may coexist, but the burden of proof rests on the diagnostician.

Treatment aims at the restoration of colonic function with the minimum of intervention. A bulky diet is indicated, consisting of liberal amounts of cooked fruits, including the mildly laxative fruits, such as figs, prunes and apple sauce, mashed or puréed vegetables, such as carrots, spinach, rhubarb and stewed tomatoes, the cereals, whole wheat bread and fresh salads. Coarse substances such as bran are apt to irritate the bowel. Meat is restricted or limited to one meal a day. Lubrication is used to facilitate the movements of the colonic contents. Retention enemas of from 2 to 6 ounces (59.2 to 178.0 cc.) of any of the ordinary cooking oils, such as Mazola, are extremely useful. The patient is instructed to inject this after retiring and to remain in the recumbent position after the injection. As a rule, this will be followed by an easy movement of the bowel in the morning. Oil by mouth is suggested. The liberal use of butter and olive oil in the food is recommended for the asthenic patient and mineral oil for the person who is overweight. When a spastic colon is present, tincture of belladonna, 10 minims (0.6 cc.), given three times a day for about a week, is useful. For the high-strung or nervous patient or one who fears to relinquish his habit of using carthartics or enemas, mild sedatives are given, such as phenobarbital, one-half grain (0.03 Gm.), three times a day until the apprehensiveness has subsided; the belladonna, phenobarbital or other sedatives are then discontinued. Sufficient sleep and rest are essential, and the "daily dozen" in the morning will be found useful to tone up the abdominal musculature as well as to stimulate intestinal peristalsis.

When the function of the colon is restored, intervention is discontinued, except that the retention enema of oil and the high residue diet may become more or less a permanent part of the regimen. The great majority of patients with redundant colon who are given this treatment will return to a state of approximate well-being.

CASE REPORTS

The cases are reported as instances of redundant colon in which improvement followed medical treatment. The patients were studied thoroughly to exclude, as far as possible, any other pathologic condition. In every instance a careful history was taken, a thorough physical examination was made, blood count, urinalysis, test meals for the stomach, examination of the stool and Wassermann tests were made. Fluoroscopic examinations of the chest, as well as of the gastro-intestinal tract, were made. Only the essential parts of the report are presented.

CASE 1.—W. J. D., aged 50, a physician, 5 feet and 11 inches (180.3 cm.) in height and weighing 133 pounds (60.3 Kg.), had had attacks of diarrhea since childhood. The attacks were brought on by nervous strain or physical fatigue. During the last seven years, he had had repeated attacks of diarrhea followed by constipation. The constipation usually ended by the passage of enormous stools.

Because of vague abdominal pains, atypical appendicitis had been diagnosed, and appendectomy had been performed without improvement. The periods of constipation were associated with loss of appetite and nausea. The opaque enema study showed a large redundant loop in the descending colon. Treatment as outlined was instituted and was followed by improvement.

Case 2.—M. M. C., aged 52, a woman, 5 feet and 6 inches in height (167.6 cm.) and weighing 145 pounds (65.8 Kg.), of intermediate habitus, had been con-

Fig. 3 (case W. J. D.).—Elongated loop in descending colon.

stipated and had been taking enemas and cathartics for many years. She complained of loss of strength, lassitude, gas distress, bad taste, pain in the back and in the hypochondria. The appendix had been removed and ventral suspenion of the colon had been performed. Roentgen-ray examination showed an elongated and looped transverse colon extending from the lower border of the costal margin down into the pelvis; also a marked colonic stasis as shown by

the presence of barium in the descending colon 120 hours after the ingestion of a meal of barium. The patient was placed on the treatment outlined, and considerable improvement resulted.

CASE 3.—M. K., a man, aged 26, weighing 129 pounds (58.5 Kg.) and 5 feet and 5 inches (165.1 cm.) in height, of intermediate habitus, had been constipated ever since childhood. The appendix had been removed. The patient complained of gas distress, belching and abdominal gas distress and occasional

Fig. 4 (case M. K.).—Multiple redundancies in hepatic and splenic flexures, and in the pelvic colon.

vomiting. He used cathartics frequently. The chief complaint was belching, which afforded little relief. Roentgen-ray examination showed three redundant loops: one in the hepatic flexure, one in the splenic flexure and one in the pelvic colon. The transverse colon was spastic. Treatment was instituted; within a week the patient became symptom-free and remained so for a period of several months while under observation.

Case 4.—T. Y., a man, aged 38, 5 feet and 9 inches (175.3 cm.) in height and weighing 137 pounds (62.1 Kg.), underweight 25 pounds (11.3 Kg.), of asthenic habitus, had been constipated for many years. He used cathartics and periodical enemas habitually. The appendix had been removed. The patient complained chiefly of gas distress, belching, flatulence and discomfort and occasional attacks of cramps in the lower part of the abdomen, associated with a rumbling sensation and constipation. Cathartics had failed to give relief. Occasionally large bulky stools were passed, followed by a sense of relief and comfort. Roentgen-ray

Fig. 5 (case T. Y.).—Multiple redundancies in the hepatic flexure, descending and pelvic segments of the colon.

examination showed ptosis of the entire colon, with three redundant loops: one in the hepatic flexure, one in the descending colon and one in the pelvic colon. Treatment as outlined was instituted, and considerable improvement followed.

Case 5.—G. W. R., a man, aged 44, a civil engineer, 6 feet and 2 inches (188 cm.) in height and weighing 185 pounds (83.9 Kg.) complained of a bad taste, constipation, headache and attacks of indigestion. He used cathartics habitually. The appendix had been removed. The patient also complained of gas distress, abdominal discomfort, borborygmi and lassitude. Roentgen-ray

examination showed an elongated fold with a kink in the pelvic colon. Medical treatment was instituted. Within a few weeks the patient became symptom-free, and has remained so.

Case 6.—E. S., a woman, aged 48, of intermediate body habitus, 5 feet 2 inches (157.5 cm.) in height and weighing 112 pounds (50.8 Kg.), 22 pounds (10 Kg.) underweight, complained of constipation, loss of appetite and lassitude, distress in the upper part of the abdomen, insomnia, loss of weight

Fig. 6 (case E. S.).—Reduplication of the pelvic colon which ascends in spiral fashion to lie in contact with the ptosed transverse colon.

and strength. She had used cathartics and enemas for many years. Roentgen-ray examination showed a redundant loop beginning in the lower portion of the pelvic colon and ascending by a spiral loop to the upper brim of the pelvis, where it lay in contact with the transverse colon which was ptosed. The patient was given the high residue diet and instructed to use rectal enemas of oil. Considerable improvement resulted.

Case 7.—J. G., a man, aged 31, 5 feet and 8 inches (172.7 cm.) in height and weighing 134 pounds (60.8 Kg.), of asthenic habitus, was 20 pounds (9 Kg.)

underweight. He complained of distress in the upper part of the abdomen not related to the taking of food, occasional headaches, constipation for eight years, loss of appetite and of strength. He used cathartics continually. Abdominal consciousness was present most of the time, and there were borborygmi and occasional severe attacks of abdominal pain, which were relieved by the free passage of flatus. Roentgen-ray examination showed the presence of an atonic

Fig. 7 (case J. G.).—Redundant loop in the pelvic colon associated with dilated and atonic ascending colon.

and dilated ascending colon and a pronounced redundant pelvic loop. Rapid improvement followed the treatment outlined.

Case 8.—O. S., a man, aged 58, of asthenic habitus, 5 feet and 8 inches (172.7 cm.) in height and weighing 111 pounds (50.3 Kg.), was 52 pounds (23.6 Kg.) underweight and inclined to minimize his symptoms or even to deny their existence. His family became alarmed over his progressive loss of weight,

and overruled his objections to physicians. He said that he had been constipated all his life, passed small, hard stools, had attacks of violent abdominal pain, not localized but general in its distribution, and distressing attacks of gas pains. When I first saw him, the patient was doubled up with intense abdominal pain, yet he insisted that there was nothing the matter. Roentgen-ray examination showed a redundant colon, with two marked redundant loops, the most pronounced I have ever encountered, located in the transverse and pelvic colons. The transverse

Fig. 8 (case O. S.).—Extreme type of redundancies. The true ascending and descending segments were filled with gas and failed to cast suitable shadows. The "transverse" segment is replaced by a descending segment and continued as ascending oblique segment, while the pelvic segment traverses the pelvis to descend on the right side instead of the usual left side.

colon did not exist as such; it was replaced by a V shaped segment, the first part of which descended directly in front of the true ascending colon down to within the pelvic brim, then it ascended by a left oblique segment to the splenic flexure. The pelvic colon began at its usual place on the inner left side of the

pelvis, then instead of descending on the left side, it traversed the pelvis and descended on the right side. The patient's response to treatment was most gratifying. Within a few days, he became symptom-free, and in six weeks (at the time of this writing) he had gained 22 pounds (10 Kg.).

CASE 9.—J. Q., a woman, aged 51, 5 feet and 4 inches (162.6 cm.) in height and weighing 125 pounds (56.7 Kg.), of intermediate body habitus, complained of constipation of seven years' duration. She took an enema each night. She complained principally of gas distress, flatulence, belching and intestinal rum-

Fig. 9 (case H. A.).—Multiple redundancies in the splenic flexure and in the pelvic colon, associated with marked ptosis.

blings, occasional attacks of nausea and vomiting, headaches and vague pains in the left lower quadrant of the abdomen. Roentgen-ray examination showed the presence of a redundant loop in the pelvic colon and a spasticity of the transverse and descending colons. Treatment was followed by marked improvement.

CASE 10.—H. A., a woman, aged 46, 5 feet and 3 inches (160 cm.) in height and weighing 125 pounds (56.7 Kg.), of asthenic habitus, had been constipated all her life and had used cathartics and enemas habitually. Within a few months before she consulted me, they had lost their potency, and the patient

suffered from headaches, loginess, lassitude, gas distress and pains in the lower part of the abdomen. The appendix had been removed. The failure of the bowel to function was causing the patient considerable mental anxiety. She belched a great deal but obtained little relief from it. Roentgen-ray examination showed that almost the entire transverse colon was below the crests of the ilia, while both the hepatic and the splenic flexures reached only to the level of the umbilicus. Redundant loops were present in the splenic flexure and in the pelvic colon. Considerable improvement followed medical treatment.

Case 11.—M. A. N., aged 45, a physician, 5 feet and 10 inches (177.8 cm.) in height and weighing 170 pounds (77.1 Kg.), of intermediate body habitus, considered himself neurotic and inclined to introspection. He had always had more or less stomach trouble. As a medical student he had been treated for

Summary of Author's Series of Cases of Redundant Colon

Case	Age	Sex*	Body Weight, Pounds	Body Height	Body Habitus	Previous Operations	Location of Redundancy	Result of Medical Treatment
1	50	♂	133	5 ft. 11 in.	Asthenic	Appendectomy	Descending	Improved
2	52	♀	145	5 ft. 6 in.	Intermediate	Appendectomy, ventral suspen- of colon	Transverse	Improved
3	26	♂	129	5 ft. 5 in.	Intermediate	Appendectomy	Hepatic flex- ure, splenic flexure, pelvic	Improved
4	38	♂	137	5 ft. 9 in.	Asthenic	Appendectomy	Hepatic flex- ure, descend- ing, pelvic	Improved
5	44	♂	185	6 ft. 2 in.	Intermediate	Appendectomy	Pelvic	Improved
6	48	♀	112	5 ft. 2 in.	Intermediate	.....	Pelvic	Improved
7	31	♂	134	5 ft. 8 in.	Asthenic	.....	Pelvic	Improved
8	58	♂	111	5 ft. 8 in.	Asthenic	.....	Pelvic, trans- verse	Improved
9	51	♀	125	5 ft. 4 in.	Intermediate	.....	Pelvic	Improved
10	46	♀	125	5 ft. 3 in.	Asthenic	.....	Pelvic, splenic flexure	Improved
11	45	♂	170	5 ft. 10 in.	Intermediate	Appendectomy, laparotomy	Pelvic	Improved

* In this table ♂ indicates male; ♀, female.

hyperacidity; he then had had his appendix removed and another laparotomy had been performed. He had always been constipated, and at one time his condition had been diagnosed as ulcer, for which he had been treated. He complained of constipation, gas distress and bad taste. He used cathartics continually. The most annoying symptom was the gas distress, which became so acute at times as to interrupt his social hours. He sought relief by walking, and felt better following the expulsion of flatus. Roentgen-ray examination showed a marked redundant loop in the pelvic colon. This redundancy and its significance apparently had been overlooked. Improvement followed medical treatment.

EVOLUTION

Judging by the repeated attacks launched against the mechanism of the colon, it is easy enough to gain the impression that nature erred in her attempt at the construction of the colon. With all the discussions raging about the stasis of the colon, it might appear that nature stands

indicted for having constructed a colon so prone to faulty behavior; perhaps an overdevelopment of an anatomic form—an error of the type of the *Amphibious apatosarus,* a colossal reptilian monster that roamed the shores of the great inland sea in what is now Colorado about 30,000,000 years ago. This colossal monster did not survive in the struggle for existence; its size was against it, and it went the way of *Archeopteryx* and the saber tooth tiger. But man is an egocentric animal. He is prone to stand on the shores of the Atlantic, of the Pacific, or of the Tigris, or within the castled walls of Potsdam and look about him for more worlds to conquer. He is likely to consider himself the center of the universe, and that everything was made for his pleasure; he even vents his wrath on all things that incur his displeasure and destroys those that oppose his will. Yet, from an evolutionary point of view, man represents but a single phase of a constantly changing biologic cycle. Perfect or an experiment, man represents but an attempt of nature at a combination of biologic forces. The length of his survival is a matter of speculation.

If he has a lengthy colon, it is because he needs it. If it seems too long, it but appears lengthy because of his artificial domesticated form of existence. In the primeval forest where man lived at the time the colon was evolved, it was necessary and extremely useful. The colon represents one of nature's finest handiworks in the development and protection of her favored children. From an evolutionary point of view, the colon is partly a protective mechanism. When man descended from the trees and began to roam the plains and forest, he was pursued by his natural enemies, just as he sought their flesh as food. The excreta of an animal with its characteristic odor is one of the signs by which an animal stalks its natural prey. The species that ejects its excreta but once a day is better prepared to escape its enemies, and so survive in the struggle for existence, than the less fortunate animal that ejects its excreta more frequently, and the colon which performs this function is a proud masterpiece of protective mechanism. In the early days, the colon served *Pithecanthropus erectus* of Java well. It enabled him to escape from his natural enemies, and so it was an essential factor in his successful struggle against his environment. But man no longer roams the primeval forest; instead, he sits at a desk all day and dictates letters. He eats ham sandwiches on white bread with the crusts carefully removed and ice cream, and he drinks iced tea. In the evening he goes to the "Follies" and on Sunday afternoon he plays golf, perhaps. His diet is residue-free, with all the roughage painstakingly removed. The flour he eats represents the quintessence of refinement until all the salts, as well as all the roughage, have been thrown away. He leads a sedentary existence with all muscular activity carefully eliminated by

labor-saving machines, and even the use of legs, that essential to all forms of progressive animal life, a system of locomotion, is displaced by the faster arriving automobile—and the colon appears too lengthy.

SUMMARY

The redundant colon is one that is too long for its owner.

It is congenital in origin.

It is not materially influenced by the factors of age, sex or body habitus.

It is an organic structure, which develops functional characteristics; hence, the symptoms may develop any time during the life of the patient.

The chief symptoms are constipation, gas distress and abdominal pain and their attendant evils.

The diagnosis is suggested by a history of malfunction of the colon, and is confirmed by roentgenograms which show the redundancy.

Symptomatic redundant colon must be differentiated from chronic and atypical appendicitis, from gallbladder disease and from other abdominal disorders.

The treatment aims at the restoration of the function of the colon with the minimum of intervention.

A high residue diet and lubrication both by mouth and by rectum are the basis of the treatment. Antispasmodics and sedatives are useful accessories.

Surgical intervention has a place of minimum importance in the cycle of the redundant colon.

Under proper medical care, the great majority of persons with redundant colon promptly return to an approximate state of well-being.

EXTRARENAL VENOUS CIRCULATION IN A CASE OF CONGENITAL POLYCYSTIC KIDNEYS

AN UNUSUAL VARICOCELE COMMUNICATING BETWEEN THE SPLENIC AND RENAL VEINS*

EMILE DUSKES, M.D.

BALTIMORE

Congenital polycystic kidneys have always been of unusual interest. Though the clinical features and pathology of this condition are amply covered in medical literature, relatively little attention has been given to the collateral venous circulation.

The pathology of the congenital polycystic kidney is well known, and the theories of its etiology are summarized by Gruber [1] in three main hypotheses: the supposition of an inflammatory origin (Virchow, Beckman, Hertz), the neoplastic conception (von Michalowicz, Chotinsky, Lejars, Köster, Nauweck and Hufschmidt) and the theory of a congenital defective development (Witte, von Mutach, Borst, Staemmler).

The recent work of Kampmeier [2] is noteworthy. In the study of kidneys in consecutive embryonic and fetal stages, he finds that dilatations and cysts occur frequently between the convoluted tubules and the collecting ducts, and concludes that a period occurs in fetal life that is normally characterized by the presence of numerous cystic renal tubules. If the tubules fail to give way at the end of the allotted time, they may be converted into cysts. A study of general embryonic progressions and regressions makes this explanation seem plausible.

In this type of renal disease, the congenital origin of which is accepted by most investigators, it is reasonable to expect abnormalities of the renal and perirenal circulation. Oertel [3] emphasizes the fact that in the normal organ the structure is continually changing.

Gross [4] has pointed out that there is a reorganization of the arterial blood supply in pathologic conditions of the kidneys. Kuprijanoff [5] has

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* From the Department of Pathology, University of Maryland School of Medicine.

1. Gruber, G. B.: Missbildungen der Niere, Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1927, pt. 3, p. 161.

2. Kampmeier, O. F.: A Hitherto Unrecognized Mode of Origin of Congenital Renal Cysts, Surg. Gynec. Obst. **36**:185, 1923.

3. Oertel, Horst: Post-Natal Development and Pathological Organ Reconstruction in Relation to Function and Disease, Am. J. M. Sc. **161**:694, 1921.

4. Gross, L.: Studies on the Circulation of the Kidney in Relation to Architecture and Function of the Organ in Health and Disease, J. M. Research **36**:327, 1917 and **38**:379, 1918.

5. Kuprijanoff, P. A.: Das intrarenale arterielle System gesunder und pathologischer Nieren, Deutsche Ztschr. f. Chir. **188**:206, 1924.

also noted modifications in the intrarenal arterial system in normal and in diseased kidneys.

Of particular interest in this communication is the study of the readjustment or adaptation of the extrarenal or collateral venous circulation. Communications normally exist between the intrarenal and extrarenal circulation. Kölliker [6] has described branches breaking through the renal cortex and anastomosing with the capsular vessels; he speaks of them as the "rami capsularis." Hyrtl [7] describes these as the perforating branches; Poirier and Charpy [8] call them the "veines émergentes of Verneuil."

The renal vein is not a closed system. Poirier and Charpy discuss three main collateral circulations: (1) "veines émergentes of Verneuil," which pass from the substance of the kidney and enter the inferior vena cava, the lumbar or the spermatic veins and which are especially seen on the posterior surface near the hilum of the kidney; (2) "veines adipeuses," which circumscribe and receive blood from the fatty capsule and through small venules from the surface of the kidney and which communicate with the adjacent veins, such as the renal, capsular, spermatic, inferior phrenic, ureteric and lumbar, and (3) the "anastomosis réno-azygo-lumbar," which consists of a large trunk from the posterior aspect of the renal vein, communicating with the lesser azygos (hemiazygos) and the first lumbar vein.

Cruveilhier [9] found anastomosing branches between the left renal and the superior mesenteric veins. The venous anastomoses about the kidney have been separated into five essential groups by Tuffier and Lejars,[10] as follows: capsular renal, capsular mesenteric, capsular suprarenal, capsular spermatic or ovarian and capsular lumbar (fig. 1).

Geberg [11] injected the kidneys of dogs and cats and confirmed the foregoing conclusions. Liek [12] observed that the most important anastomosis in man occurred among the renal, ureteric and suprarenal

6. Kölliker, A.: Handbuch der Gewebelehre des Menschen, ed. 5, Leipzig, Wilhelm Engelmann, 1867, p. 505.

7. Hyrtl: Das Nierenbecken der Säugetiere und des Menschen, Denkschriften der K. Akademie, Wien, 1872. Quoted by Dehoff, E.: Die arteriellen Zuflüsse des Capillarsystems in der Nierenrinde des Menschen, Virchows Arch. f. path. Anat. **228**:134, 1920.

8. Poirier and Charpy: Traité d'anatomie humaine, Paris, Masson et Cie., 1901, vol. 11, pp. 994, 1014.

9. Cruveilhier, J.: Anatomie descriptive, Paris, Bechet Jeune, 1834, vol. 3, p. 306.

10. Tuffier and Lejars: Les veines de la capsule adipeuse du rein, Arch de physiol. norm. et path., series 5, **3**:41, 1891.

11. Geberg, A., quoted by Dehoff: Ueber direkte Anastomosen zwischen Arterie und Vene in der Nierenkapsel, Internat. Monatschr. f. Anat. u. Physiol., vol. 2.

12. Liek, E.: Die arteriellen Kollateralbahnen, Virchows Arch. f. path. Anat. **220**:275, 1915.

venous branches. In recent autopsies I have been able to corroborate these various anastomoses, and, in addition, I have traced minute communications between the renal vein and the pancreatic and splenic venous systems.

The veins have been brought into prominence by various methods in experimental conditions. Thus, Buchwald [13] and Litten,[14] in attempting to produce contracted kidneys in dogs and rabbits by venous occlusion, discerned that the organ decreased in size and that an abundant collateral circulation was established. During the course of a series of experiments in the study of the pathogenesis of hydrone-

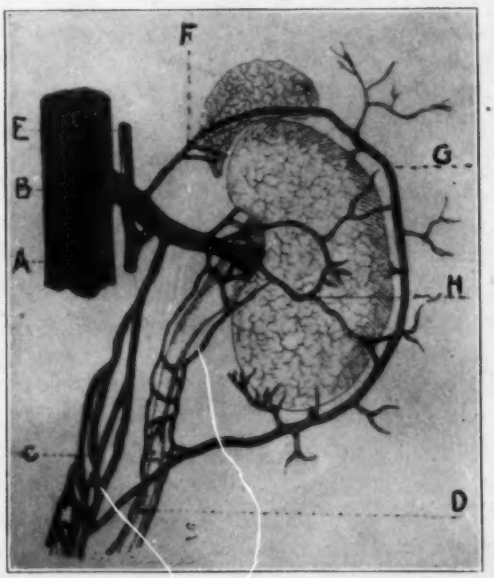

Fig. 1.—The normal collateral venous circulation (from Poirier and Charpy, after Tuffier and Lejars). *A* is the vena cava inferior; *B*, the vena renalis; *C*, the plexus venosus ovaricus (spermaticus); *D*, the plexus venosus uretericus; *E*, the vena phrenica inferior (anastomose réno-azygo-lumbar); *F*, the vena suprarenalis; *G*, the arcus venosus perirenalis, and H, the vena capsularis anterior.

phrosis in dogs in which the ureter was ligated, Lindemann [15] noted that when the kidney was enucleated or shelled out from its capsule, marked bleeding took place from the branches arising from the suprarenal,

13. Buchwald, A.: Ueber die Structurveränderungen der Niere nach Unterbindung ihre Vene, Virchows Arch. f. path. Anat. **65**:145, 1876.

14. Litten, M., quoted by Liek.: Virchows Arch. f. path. Anat. **220**:275, 1915.

15. Lindemann, W.: Ueber Veränderungen der Vascularisation der Niere bei Harnleiterunterbindung, Centralbl. f. allg. Path. u. Path. Anat. **6**:195, 1895.

lumbar and internal spermatic arteries. He observed that the veins were prominent, and, by injection and microscopic examination, he found a renal capsular venous anastomosis in the cortical substance. Similarly, Barney [16] noted that a complete and sudden obstruction of one ureter by ligation results in hydronephrosis of that kidney, and that in all cases the fibrous capsule is overlaid by a network of engorged veins not observed at the time the ureter is ligated. These veins anastomose with the spermatic or ovarian veins, the suprarenal and two or three lumbar veins posterior to the kidney. Zeckwer [17] has concluded that there is a postglomerular venous anastomosis connecting the glomeruli with the extrarenal collateral channels.

Anatomic and experimental evidence proves the existence of a definite collateral circulation. The extrarenal system and its correlation to disease has received scant attention in the examination of human kidneys.

In a case of carcinoma of the kidney, Leudet [18] observed that the left renal vein was obliterated at its point of junction with the inferior vena cava. He also said:

> The enveloping capsule was crossed by a large lacework of venous branches which exceeded in width a bird's feather and were most numerous on the inferior aspect of the kidney. These veins were continuous with large veins below the lumbar muscles and further down, with veins of the integument of the abdominal parietes. Two slightly dilated veins, larger than the median cephalic, followed the course of the ureter in passing to the surface of the renal pelvis. In the interior of the kidney, venous branches were uniformly dilated.

Abnormalities in the collateral venous circulation have not been emphasized in the study of congenital polycystic kidneys, although photographs of some of the recorded cases, showing abnormally prominent veins in the fibrous capsule, may be found in articles by Maier [19] and by Davis [20] (fig. 6 in Davis' article). In the case herein reported, there was an excellent opportunity for the study of the collateral venous circulation as observed in a case of congenital polycystic kidneys.

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16. Barney, J. D.: The Influence of the Venous Collateral Circulation of the Kidney on Hydronephrosis, Ann. Surg. **65**:597, 1917.

17. Zeckwer, I. T.: The Persistence of the Glomerular Circulation Following Occlusion of the Renal Vein of One Kidney in the Cat, Am. J. Path. **2**:57, 1926.

18. Leudet, E.: Recherches sur l'oblitération complète de la veine rénale et le mode de rétablissement de la circulation collatérale, Gaz. méd. de Paris, p. 797, 1862. Quoted by Tuffier and Lejars: Arch. de physiol. norm. et. path. **3**:41, 1891.

19. Maier, O.: Die echte polycystische Niere, ihre Aetiologie und chirurgische Behandlung, Arch. f. klin. Chir. **132**:226, 1924.

20. Davis, G. E.: Congenital Polycystic Kidneys, Am. J. Obst. & Gynec. **9**:758, 1925.

REPORT OF CASE

History.—A colored woman, aged 45, gave the anamnesis frequently associated with this type of lesion of the kidney. She had had the usual diseases of childhood; she had had typhoid fever at the age of 13 and had shown clinical symptoms of syphilis. At autopsy there was gross evidence of syphilis, and the Wassermann reaction was positive. She had had ten pregnancies, four of which resulted in miscarriages. The other six resulted in living children, of which one survived. Death resulted from renal insufficiency. The polycystic condition of the kidneys was entirely unsuspected.

Autopsy.—Typical bilateral congenital polycystic kidneys were found at autopsy. The right kidney was matted down by surrounding adhesions to the gallbladder, liver and ascending colon, which complicated study of its vas-

Fig. 2.—The anomalous vessel is seen crossing the upper third of the left kidney. The folds of the lienorenal ligament have been removed, exposing the varicocele between the renal and splenic veins.

cular system. The veins and venules on the left side were somewhat more prominent than usual, but particularly interesting was a marked enlargement of a capsular branch traversing the anterior aspect of the kidney, joining the splenic and renal veins and emptying into the latter by a triple base. In the lienorenal ligament, a marked tortuosity was found, a definite variocele (fig. 2).

The right kidney was surrounded by a thickened peritoneum adherent to the gallbladder, liver and hepatic flexure, and the perirenal fat was markedly indurated. The vessels of the right kidney were prominent and numerous, but no vascular changes or anomalies were evident (fig. 3). The surface veins of the left kidney were prominent, and the fatty capsule contained numerous dilated veins. The lienorenal ligament was enlarged, and a definite varicosity

connected it with the splenic and renal veins. Minute twigs connected the inferior surface of the diaphragm with the spleen and the colon. Engorged venules extended from the kidney to the parietes and to the posterior abdominal wall. Both kidneys, the spleen, part of the pancreas and part of the diaphragm, together with the large vessels, were removed en masse.

The kidneys presented the typical appearance of congenital polycystic disease. The right kidney measured 11.6 by 6.2 cm. and was from 5.2 to 6.4 cm. thick. The general conformity was oval. The surface was unevenly covered with innumerable large and small cystic elevations which varied in diameter from 1 mm. to 1.8 cm. and in color from a clear serous to light straw brown, intense brown mahogany or even to Indian red or blue. Resistant, firmer, more solid areas were irregularly scattered over the surface. The renal capsule was thin and was separated with difficulty from the underlying surface.

On section the cysts had a smooth, glistening lining. They were present everywhere, with only scattered areas of renal parenchyma remaining, especially near the extremities. The contents of the cysts varied from a thin, watery

Fig. 3.—Section of the right kidney, showing the typical congenital polycystic kidney. Note the cysts of various dimensions, the absence of a renal cortex, the small remains of renal parenchyma and the distorted calices.

substance to a colloid. There was no differentiation into cortex and medulla. The cysts involved the whole structure. The pelvis and calices were definitely flattened and compressed somewhat irregularly. The ureter was normal.

Many enlarged venules and a few minute perforating twigs overlay the fibrous capsule. The renal vein and artery were normal.

The left kidney was similar, and measured 11.8 cm. in length, from 5.4 to 6.3 cm. in width and from 4.1 to 7.2 cm. in thickness. An examination of this organ (with its blood vessels) showed a distinct venous anomaly. Arising from the renal vein through three branches at a point 1.6 cm. from the renal pelvis, there was a large flattened vein, which measured 1.2 cm in diameter. This vein received the suprarenal vein (fig. 4), and as it traversed the upper third of the kidney in a somewhat elongated horizontal S manner, it also received branches from the fibrous and fatty capsules. About the center of this renal course, a large branch measuring 3 mm. in diameter coming from the

surface of the kidney emptied into the inferior border. The vein passed into the lienorenal ligament and was held in its folds. Here the vein was tortuous and wormlike. It received a small branch from the lower pole of the spleen, minute twigs from the pancreas and diaphragm and numerous venules from the perirenal adipose tissue. It communicated with the splenic vein at a point 1.2 cm. from the hilum of the spleen.

For a distance of 4 cm. from the junction with the splenic vein, the anomalous vessel continued as a single trunk measuring 0.8 cm. in diameter.

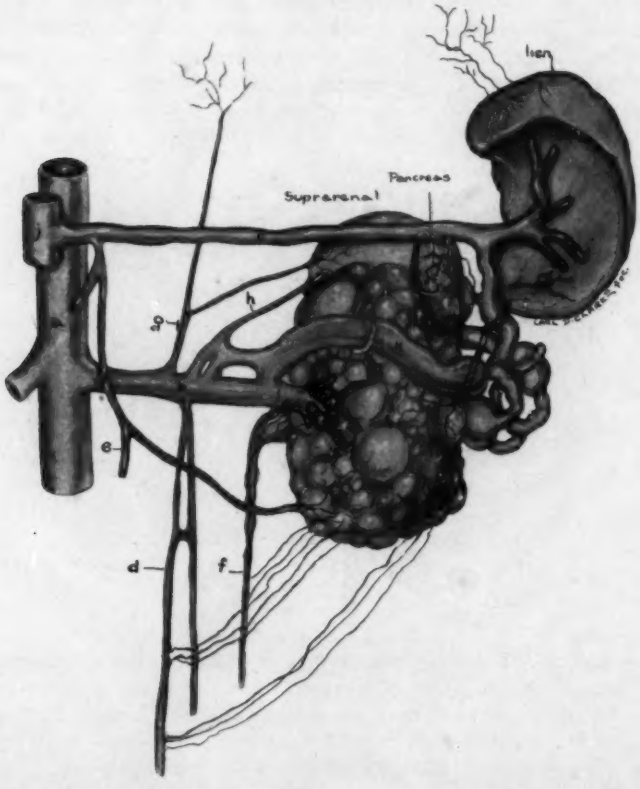


Fig. 4.—Semischematic drawing illustrating the more important vessels and the collateral anastomoses; *a* is the vena cava inferior; *b*, the vena renalis; *c*, the vena lienalis; *d*, the plexus venosus ovaricus (spermaticus); *e*, the vena mesenterica inferior; *f*, the plexus venosus uretericus; *g*, the vena phrenica inferior (anastomose réno-azygo-lumbar)); *h*, the vena suprarenalis; *j*, the vena portae, and *k*, the anomalous vein.

Here it bifurcated into two channels, both measuring 15.3 by 0.5 cm. (fig. 5). At the margin of the kidney, these channels united into a single vessel 9.2 cm. in length. The total length of the varicocele from the renal to the splenic vein was 38.5 cm. Throughout its course the vessel was tortuous and irregular, with large knoblike dilatations frequently interposed.

From the capsule of the kidney many fine vascular branches crossed the surface, but they were chiefly at the sides and margins, extending in devious directions. A few small branches entered the suprarenals at the upper pole. A few small venules arose from the surface of the hilum and emptied into the anomalous vein. In addition, capsular branches reached and accompanied the ureter. The lower pole of the kidney sent branches along the course of the ureter and to the ovarian vein. A branch went to the inferior mesenteric vein to join the splenic before emptying into the portal vein. Capsular vessels in the lateral border were traced to the diaphragm.

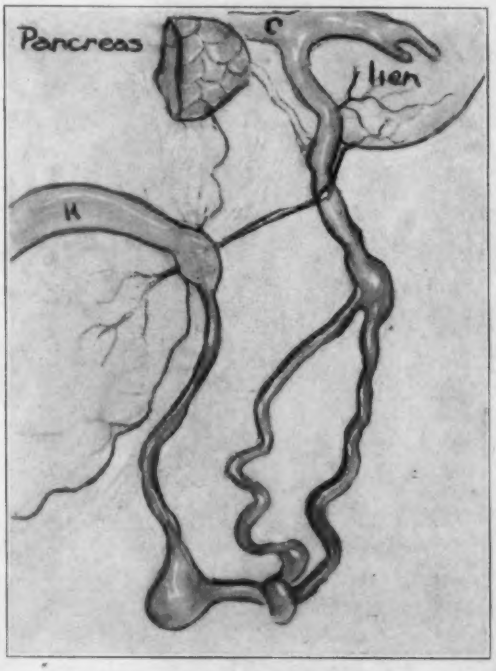


Fig. 5.—The varicocele spread out to show its form and comparative size.

SUMMARY

A case of congenital polycystic kidneys is reported. No general abnormality was present, but in a study of its collateral venous circulation, a hitherto unrecorded condition was found, a varicocele communicating between the splenic and renal veins. I believe that this condition arises as an early embryonic adjustment for a deranged venous supply. It begins as a normal minute communicating twig between the capsular and splenic venules and becomes abnormally large. Through

this reasoning the condition is explained, not only as a persistence of a normal condition, but also as an ontogenetic or antenatal accommodation to changes in morphologic structures. Anomalies have been observed repeatedly in congenital polycystic kidneys. In this case neither skeletal nor visceral tissues showed demonstrable deviations, with the single exception of this vascular monstrosity.

THE BILATERALITY OF THE LIVER

ARCHIBALD H. McINDOE, M.B., CH.B. (N.Z.)
AND
VIRGIL S. COUNSELLER, M.D.
Fellows in Surgery, The Mayo Foundation
ROCHESTER, MINN.

Since the statement of Duvernoy,[1] in 1835, that the number of lobes in the liver described by different authors was truly remarkable, there have been many further plans proposed for dividing this organ into separate anatomic areas. At the present time the majority of modern textbooks describe the liver as consisting either of two lobes separated by the falciform ligament, or of some variation of the familiar "five lobes, five surfaces and five fissures." A review of the literature will easily convince one that the question has been considered from different standpoints with just as diverse results, so that a correlation of the various embryologic, anatomic and morphologic conceptions is rather difficult. We shall review in some detail the literature on the subject, and present evidence of an anatomic and pathologic nature which may aid in its solution.

HISTORICAL REVIEW

Duvernoy[1] (1835), from a comparative anatomic study, concluded that the mammalian liver was composed of a principal lobe divided into two or three subsidiary parts, and lying between a right and a left lobe. This plan was somewhat modified in the liver of man, so that only a principal lobe remained with a prominence equivalent to the right lobule on its lateral surface. He held that the chief factors in the variation of the lobes and fissures were the character of the food and the correlated configuration of the stomach. Rolleston[2] (1861) proposed to speak of the liver as divided into three parts, the right, left and suspensory lobes, using the suspensory or falciform ligament as a center of division. This landmark has been almost universally used by subsequent investigators.

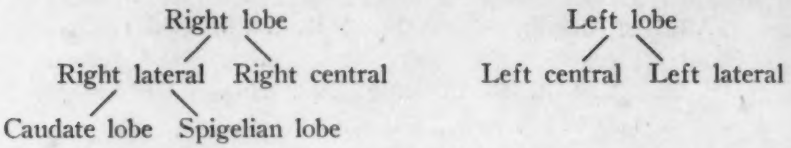
Flower[3] (1872), after studying livers from almost every variety of mammal, made perhaps the first really important contribution to the subject. Following Rolleston, he considered the liver to be pri-

1. Duvernoy, quoted by Bradley: J. Anat. & Physiol. **73**:259, 1909.

2. Rolleston, G.: On the Homologies of the Lobes of the Liver in Mammalia, Brit. Assn. Rep. Notices and Abstracts, 1861, p. 174.

3. Flower, W. H.: Lectures on the Comparative Anatomy of the Organs of Digestion of the Mammalia, M. Times & Gaz. **1**:291, 392, 451, 507, 561, 621, 678; **2**:19, 59, 115, 319, 371, 427, 591, 645; 1872.

marily divided by the remains of the umbilical vein and ductus venosus into the right and left halves. Each half was then subdivided thus:



Four principal lobes were thus recognized with the caudate and spigelian lobes attached as appendages to the right lateral subdivision. Flower found that the liver in all mammals, except the gorilla, resembles that of man to a fairly great extent. The differences in the gorilla caused him to note either that the modifications of the liver are not characteristic in related animals, or that the gorilla ought not to occupy the position in the evolutionary system hitherto accorded to it.

Rex [4] (1888) considered the arrangement of the blood vessels within the liver in relation to the form of the organ as a whole. Independently, he confirmed the work of Flower, although his use of a different terminology makes a clear understanding of his meaning somewhat difficult. He found that the right and left branches of the portal vein had a remarkably regular distribution by means of secondary branches within the liver, not only in man, but in related animals. Therefore, he felt he could trace the process of development not only through the lobes, but also through the branches of the portal vein. The following scheme shows the relation of vessels to lobes according to Rex:

- Right main portal vein
  - Ramus descendens, supplying caudate lobe
  - Ramus cysticus, supplying right central lobe
  - Ramus arcuatus, supplying right lateral lobe
- Left main portal vein
  - Ramus omentalis supplying omental lobe
  - Ramus angularis supplying left lateral lobe
  - Recessus umbilicalis
    - right arborization supplying right central lobe
    - left arborization supplying left central lobe

This arrangement is practically the same as that of Flower, except that the term omental is used for spigelian. Here again the falciform ligament was used to divide the liver primarily into halves. Rex did not attribute the presence or absence of fissures to the vessels, but stated that homologous regions of the liver in different animals may have homologous vessels whether fissures are present or not. Ruge [5]

4. Rex, H.: Beiträge zur Morphologie der Säugerleber, Morphol. Jahrb. **14**: 517, 1888.

5. Ruge, G.: Der Verkürzungsprocess am Rumpfe von Halbaffen; eine vergleichendanatomische Untersuchung, Morphol. Jahrb. **18**:185, 1891.

(1892), however, attributed the variations in the conformation of the liver to the embryologic modification in the form of the trunk and to a flattening of the dome of the diaphragm, rather than to any intrinsic influences. In the same way, Keith[6] (1899), writing of the disappearance of the fissures in man and anthropoid apes, held that as a result of the assumption of the upright posture, the dorsal mesentery has acquired a more complicated mode of fixation, consequent on the removal of the support formerly afforded the liver by the ventral abdominal wall. The more extensive fixation of the liver to the dorsal abdominal wall is thus correlated with the disappearance of the fissures. It has been pointed out several times that Keith's explanation does not show why an undivided liver is found outside of primates, in mammals with a prone position and an uncomplicated dorsal mesentery. Again, from a study of the livers of anthropoids and those of human fetuses from 2 months to full term, Thomson[7] (1899) found little on which to base definite conclusions. Like Flower, he considered that the gorilla showed the greatest subdivision, possessing separate caudate and subdivided right and left lobes. In the orang-utang and gibbon the caudate lobe also was usually separate. In the human fetus the liver was remarkable for the proportionate size and prominence of the spigelian and caudate lobes, the latter in many instances being separated from the right lobe by a deep fissure along its anterior border. He held that the appearance of anomalous fissures and clefts on the under surface of the right lobe of the liver of man could thus be accounted for by reference to the fetal condition and to the arrangements of the lobes in the anthropoids. It is noteworthy that Thomson attributed more importance to the caudate and spigelian lobes than any previous or subsequent writer.

From the embryologic aspect there is much of interest, but little that is not extraordinarily contradictory. Brachet's[8] contribution (1895) is of interest in that he recognized the fact that the lobes are developed in conjunction with the vessels. Thus, he found that the liver of the rabbit consisted essentially of three lobes: (1) a median lobe occupying the ventral portion of the organ and consisting of that part developed in conjunction with the two umbilical veins; (2) a left lateral lobe proceeding from the primitive left omphalomesenteric lobe which develops along the vein of the same name, and (3) a right lateral

6. Keith, A.: The Position and Manner of Fixation of the Liver of Primates and the Part These Factors Play in the Lobulation of the Liver, J. Anat. & Physiol. **33**:21, 1899.

7. Thomson, A.: The Morphological Significance of Certain Fissures in the Human Liver, J. Anat. & Physiol. **33**:546, 1899.

8. Brachet, G.: Recherches sur le développement du diaphragme et du foie chez le lapin, J. de l'anat. et de la physiol. **31**:511, 1895.

lobe bearing the same relationship to the right omphalomesenteric vein, with the so-called spigelian and caudate lobes as mere appendages.

In his more recent embryologic monograph, Mall[9] (1906) deals extensively with this question of lobular constitution. Admitting that the liver is primarily a bilobular organ he says:

> In the embryo of the end of the fifth week the right and left portal twigs have begun to divide, and from the recessus umbilicalis a new group of veins have formed and radiate into the middle and left lobes of the liver. On the hepatic side the left branch has divided into two trunks and two new branches have appeared: the vena cava inferior and the vena hepatica media which has its terminal right and left branches. The right omphalo-mesenteric vein is still present and the ductus venosus is well marked. In this case the liver is formed of four main lobules and with the subdivision of the middle and left hepatic veins into two branches each, six primary lobules are seen to correspond with the six primary lobes of the mammalian liver. . . . With the completion of six lobules we recognize fully the adult form of the liver. Each lobule now represents one of the six lobes of the mammalian liver; each of the primary lobules is to expand into a whole lobe.

Bradley[10] (1909) took strong exception to this last statement. He considered these so-called lobes merely arbitrary divisions of the organ made for the purposes of description, and as such they could have little anatomic value. The umbilical fissure in man and mammals was not a true fissure, in that it might be late in appearing and might even be absent in the adult. He pointed out that its occurrence depends on the presence of the left umbilical vein, and that if the right umbilical vein were to persist, two fissures would occur, thus making manifest the error of considering one of them as a dividing line in the anatomic structure of the liver. From an examination of the portal and hepatic veins in a large number of embryos of pigs, he came to the conclusion that the mammalian liver consisted essentially of three lobes: a central and two lateral. The central lobe was not divided by the falciform ligament, as Flower concluded, although otherwise their conceptions were practically identical. Comparing the nomenclature of these two writers, the following resemblances are noted:

Bradley		Flower
Central lobe		Right central lobe
Right lateral lobe	Main portion	Left central lobe
	Caudate lobe	Right lateral lobe
	Spigelian lobe	Caudate lobe
		Spigelian lobe
Left lateral lobe		Left lateral lobe

9. Mall, F. P.: A Study of the Structural Unit of the Liver, Am. J. Anat. **5**:227, 1906.

10. Bradley, O. C.: A Contribution to the Morphology and Development of the Mammalian Liver, J. Anat. & Physiol. **43**:1, 1909.

With these divisions, Bradley follows Brachet in identifying various embryonic veins, the umbilical veins arising in conjunction with the central lobe, the right and left omphalomesenteric veins with the lateral lobes.

So much for the evidence from the embryologic and comparative anatomic standpoints. Duvernoy recognized two lobes; Rolleston, Brachet and Bradley, three; Flower, four, and Rex and Mall, six. The majority of these authors allow of further subdivisions of the principal lobes, although there is little uniformity in the areas of hepatic tissue contained within their boundaries.

The physiologic and purely anatomic aspects, however, are interesting. Glénard [11] (1890), from a series of careful clinical observations, came to the conclusion that definite alterations in size, tenderness and consistency, occurred in the lower palpable border of the liver in a variety of diseases. Thus, in diabetes, the right lobe was found to be the seat of most marked change; in gastritis from alcoholism, the left lobe was most affected, and in biliary disease the central portion. From this he supposed that parts of the liver were of independent vascular supply and drained definite areas of the gastrointestinal tract. Wertheimer and Lepage [12] (1896), in the course of other experiments, found that on injecting sulphindigodate of soda into the right or left hepatic duct, no transference took place from side to side; therefore, they concluded that the right and left lobes were distinct in their biliary drainage. It remained for Cantlie [13] (1898) to state the matter clearly. After observing the liver of a Chinaman at necropsy, in which there was complete atrophy of the right lobe, due to abscess, and compensatory hypertrophy of the left lobe, he injected the portal vessels of several livers and found that the gallbladder occupied a central position in the organ with the true right and left lobes on each side of it. The line of separation ran from the fossa for the gallbladder to the entrance of the hepatic veins into the inferior vena cava. Injections into the arteries and bile duct were not so satisfactory, but on the whole were confirmatory of his hypothesis.

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11. Glénard, F.: Des résultats objectifs de l'exploration du foie chez les diabétiques, Lyon méd. **44**:5, 80, 115, 189, 259, 1890.

12. Wertheimer, E., and Lepage, L.: Sur les voies de resorption de la bile dans le foie, Compt. rend. Soc. de biol. **48**:950, 1896.

13. Cantlie, J.: On a New Arrangement of the Right and Left Lobes of the Liver, Proc. Anat. Soc. Gr. Britain & Ireland **32**:4 (June) 1898.

Sérégé [14] (1901), apparently unaware of Cantlie's communication, confirmed and extended the observations of Glénard. By the injection of methylene blue into each lobe, he showed that there was a distinct independence of blood supply in the two sides, the line of separation corresponding to that described by Cantlie. Moreover, after the injection of small amounts of India ink into the splenic and mesenteric veins and its discovery in definite situations within the liver, he stated that within the portal vein two blood currents existed, with different characteristics. These currents arose from the mesenteric area on the one hand and the splenic on the other, the former going to the right lobe and the latter to the left. He supported his theory with numerous clinical observations. This work was repeated by Glénard [15] (1901), with identical results. Sérégé [16] (1902), by determining the urea content of the right and left lobes of the liver in the dog following a meal of chopped meat given after a period of fasting, found marked differences in the urea content during the various phases of digestion. During the first two hours the left lobe contained more than the right; from the second to the fourth hour, the right contained more than the left, and at the eighth hour, the amount was the same on both sides. Silvestri [17] (1905), from the same type of experiment, confirmed the functional autonomy of the two sides of the liver to a certain extent, but considered the difference slight. Loeb [18] (1907), following the subcutaneous injection of 0.9 Gm. of potassium iodide, found that the right lobe contained much more than the left one hour after injection. This was partly confirmed by Wells and Hedenburg [19] (1912). Looten [20] (1908), using indigodate of soda and carmine as injection material in twenty-five livers obtained from cadavers, could not demonstrate an intrahepatic capillary circulation between the bile

14. Sérégé: Contribution a l'étude de la circulation du sang porte dans le foie et des localisations lobaires hépatiques, J. de méd. de Bordeaux **31**:271, 291, 312, 1901.

15. Glénard, F.: Note sur les localisations lobaires hépatiques, Bull. et mém. Soc. méd. de hôp. de Par. s. 3, **18**:386, 1901.

16. Sérégé: Sur le teneur on urée de chaque lobe du foie en rapport avec les phases de la digestion, Compt. rend. Soc. de biol. **54**:200, 1902.

17. Silvestri, T.: Sull' indipendenza funzionale ed anatomica dei lobi del fegato, Gazz. d. osp. **26**:570, 1905.

18. Loeb, O.: Die Jodverteilung nach Einfuhr verschiedener Jodverbindungen, Arch. f. exper. Path. u. Pharmakol. **56**:320, 1907.

19. Wells, H. G., and Hedenburg, O. F.: Studies on the Biochemistry and Chemotherapy of Tuberculosis: I. The Permeability of Tubercles for Iodin Compounds and Proteins, J. Infect. Dis. **11**:349, 1912.

20. Looten, J.: Contribution a l'étude de l'indépendance vasculaire du foie droit et du foie gauche. Existe-t-il ou non un double courant sanguin dans la veine porte? J. de l'anat. et de la physiol. **44**:87, 1908.

ducts of the two sides. Like Wertheimer and Lepage, he felt obliged to consider the liver of man, not as a unique and compact mass, but as formed of two lobes clearly separate and independent. Gilbert and Villaret [21] (1909), while confirming the existence of a gross independence of the two lobes, denied the absence of a capillary anastomosis in the median plane. The whole question was reviewed by Bauer [22] (1909), who, from injection experiments with India ink, concluded that it was impossible to distinguish a mesenteric and a splenic area in the liver. The so-called line of demarcation between the right and left lobes was by no means constant, representing merely a zone of union between two portohepatic venous systems such as occurs in many other places in the liver. The separation was not absolute, and injection fluids readily flowed from one side to the other. Bartlett, Corper and Long [23] (1909), however, from the absorption of emulsified fat and copper in isolated intestinal segments, considered the functional independence of the two lobes to be partially established, with some slight overlapping of the two sides. They found a dual portal current in the dog; the blood from the stomach, spleen, duodenum, first portion of the jejunum and rectum flows mainly to the left lobe, while the blood from the lower jejunum, ileum and first portion of the large intestine flows mainly to the right lobe.

PURPOSE AND SCOPE OF STUDY

In the course of a study of the blood vessels and bile ducts of a large number of normal livers of man, by means of injection of celloidin and subsequent corrosion, we were struck by the frequency with which specimens of all types fell apart along a line joining the fossa for the gallbladder to the inferior vena cava, unless the main trunks had been thoroughly hardened before the specimen was handled. As this method is admirably suited to the demonstration of vascular distribution, it has been used to investigate the question more thoroughly. A series of livers from the human cadaver have been injected through the separate branches of the portal vein, hepatic artery and bile duct in order to study the constancy of the separation and its situation with regard to the three vessels. Thus the right and left branches of the portal vein, the right and left branches of the hepatic artery, and the right and left hepatic duct were injected with different colors four

21. Gilbert, A., and Villaret, M.: Recherches sur la circulation du lobule hépatique, Arch. de méd. expér. et d'anat. path. **21**:373, 1909.

22. Bauer, A.: L'indépendence des lobes du foie est hypothèse, J. de l'anat. et de la physiol. **45**:1, 1909.

23. Bartlett, F. K.; Corper, H. J., and Long, E. R.: The Independence of the Lobes of the Liver, Am. J. Physiol. **35**:36, 1914.

times. In all, twelve livers were examined in this way, and thirty other specimens showing various combinations of injections were studied for the purpose of determining the relationship between the various systems.

METHOD EMPLOYED

The method was indentical with that previously used and described by us for injecting the hepatic vascular and biliary systems, except that contrasting colors were used in the two sides.[24] It is necessary to define clearly the limitations and possibilities of the method before discussing the results. The thickness of the injection material is so arranged that it will penetrate into the finest arterioles and venules and smallest bile ducts. The success of this can be determined by counting the number of branchings from the parent stem to the smallest radicle. In the liver this number varies between five and six, as has been shown by Mall and others. If possible, the sinusoids are not entered; if they are, a solid specimen is produced, which is useless for study. It is therefore understood that what follows is based on a study of the extrasinusoidal circulation of the liver. In considering the question of a sinusoidal circulation across the median plane, we used microscopic methods with tissue from normal livers and from the line of demarcation in cases of occlusion of single branches of the various vessels.

RESULTS

Portal Vein.—In all separate injections of the right and left branches of the portal vein with different colors, a striking and constant result was produced. The right branch was found to be distributed over an area including that portion of the liver from the right extremity to a plane passing through the middle of the fossa for the gallbladder and the point of entrance of the hepatic veins into the inferior vena cava. The left branch supplied the left half of the liver from this line of diivsion to the left extremity (fig. 1). The gallbladder lay in a cleft between the two sides, thus occupying a median position in the liver itself. Its efferent veins usually drained into the right and left branches of the portal vein, although occasionally more into one than the other; as these veins are large and anastomose freely over the surface of the vesicle, this arrangement varied considerably with the injection. Contrary to the generally accepted view, it was usually found that two rami omentales supplied the spigelian lobe, one arising from each branch of the portal vein. The line of division thus practically always splits the spigelian lobe into two equal and longitudinal portions. In order to

24. Counseller, V. S., and McIndoe, A. H.: Dilatation of the Bile Ducts (Hydrohepatosis), Surg. Gynec. Obst. **43**:729, 1926.

examine this plane of separation more carefully and to make sure that no anastomotic branches crossed the median line, injections of single branches were made, with the result that each side was found to be an independent anatomic unit. The contiguous surfaces of the two sides were composed of tiny branches identical with those occurring on the outer surface of the organ. Many large branches could be seen coming

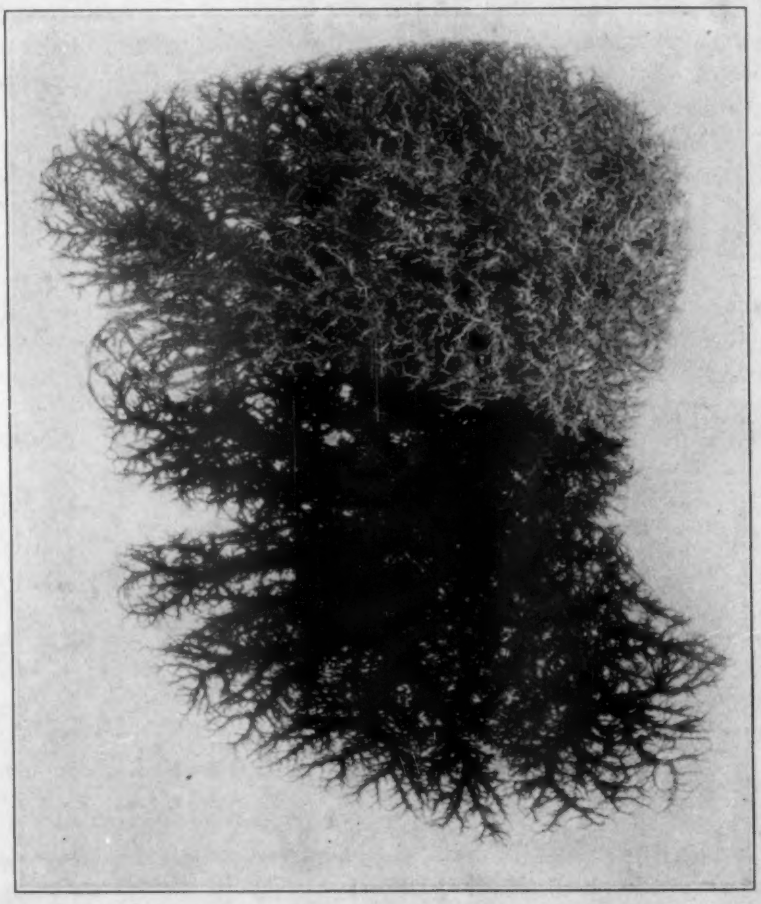

Fig. 1.—Injection of celloidin in the right and left branches of the portal vein. Note the relation of the line of separation and the fissure for the falciform ligament. Superior view.

to the surface and then turning aside, breaking up into a series of small veins in stellate fashion, as though they had suddenly encountered an invisible obstacle. No such clearly definite area existed in any other portion of the portal venous tree; the smaller radicles freely intermingled so as to make their separation practically impossible. This would effec-

tively dispose of the view that the line of separation represents merely the division between two portohepatic venous systems. The following scheme represents the named branches contained in the two main divisions:

- Right portal vein
  - Ramus arcuatus
  - Ramus cysticus
  - Ramus descendens
  - Right ramus omentalis
- Left portal vein
  - Left ramus omentalis
  - Ramus angularis
  - Recessus umbilicalis
    - Left arborization
    - Right arborization

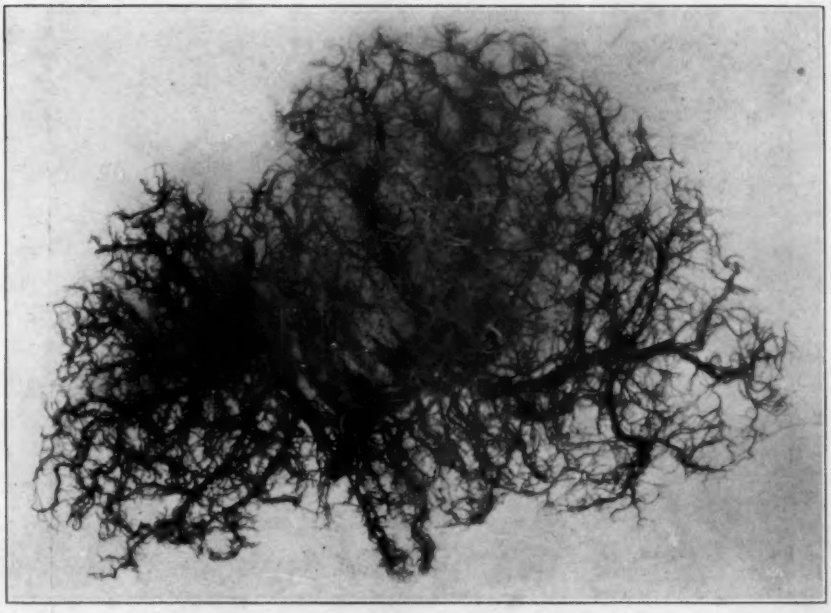

Fig. 2.—Injection of celloidin in the right and left branches of the hepatic artery. Superior view.

As has been previously pointed out, however, many of these named branches are of no greater importance in point of size than unnamed ones that accompany them. The ramus angularis, for instance, is only one of the many large branches that supply the lateral portion of the left lobe. The ramus arcuatus and ramus descendens also are representative of groups rather than single channels. It seems, therefore, somewhat unwarranted to ascribe to them alone the rôle of blood channels to definite lobes of the liver, and to divide the organ anatomically on that basis.

Hepatic Artery.—Here, too, it was possible to show a definite line of separation between the right and left branches corresponding entirely

in situation and characteristics to that in the portal vein (fig. 2). In the four cases in which the two sides were injected, and in others in which combinations of artery-vein and artery-bile duct were made, the line of division was found to be constant; however, certain slight differences were noticeable. In the portal vein the separation outside the sinusoidal circulation was found to be absolute, not even venule-sized trunks crossing the boundary. In the artery, as has been noted, there was a marked tendency to an arteriolar anastomosis, both in the capsular plexus on the surface of the liver and in the vaginal plexus in the portal spaces. It was therefore not surprising to find that a slight arteriolar anastomosis existed from side to side, sufficient to show a little mixing of the two colors. It was most easily seen between the capsular vessels of the two sides, but even at its best the transference was slight. As with the vein, each branch sent a twig to the spigelian lobe and then broke up into its terminal divisions, corresponding in distribution to those of the portal vein, with which they remained closely related.

Bile Ducts.—Injection of the right and left hepatic duct was rather more difficult to carry out because the point of division of the common hepatic duct is slightly higher in the hilum of the liver. The passing of a ligature round the cannulas is extremely likely to rupture the hepatic tissue and damage the vasa aberrantia in this situation, with consequent leakage which is difficult to control. With care, however, satisfactory specimens were obtained, which demonstrated beyond doubt that the biliary drainage of the liver is anatomically as distinctive as its vascular supply.

Here again the line of demarcation coincided entirely with that described for the portal vein and hepatic artery (fig. 3). Whatever pressure was employed, anastomosing branches could not be demonstrated between the two sides, even in specimens in which the fifth and sixth orders of branchings had been reached. A slight transference occasionally took place in the cleft formed by the right and left hepatic ducts, by way of the vasa aberrentia, where, as is well known, a slight communication from side to side may occur by means of these vestigial structures. This must be regarded as an extrahepatic site, and Kiernan and others [25] probably found that injection fluids pass from right to left by this route. In order to show the complete absence of cross-anastomosing vessels more convincingly, a case of obstruction in the common duct by carcinoma of the head of the pancreas was chosen in which there was marked hydrohepatosis. The two sides were injected sepa-

25. Kiernan, F.: The Anatomy and Physiology of the Liver, Phil. Tr. Roy. Soc. London, 1833, p. 710.

rately and at different times, but even with such huge dilatation as had occurred, no channels were opened between the two sides.

Since the smaller branches of the bile ducts accompany the portal vein and hepatic artery, they will bear the same general relation to the hepatic parenchyma. When the portal vein, hepatic artery and bile ducts were injected simultaneously, the plane of separation of their right and left branches was common to all three (fig. 4).

To summarize: The liver is divided into two more or less equal parts by a line from the center of the fossa for the gallbladder to the

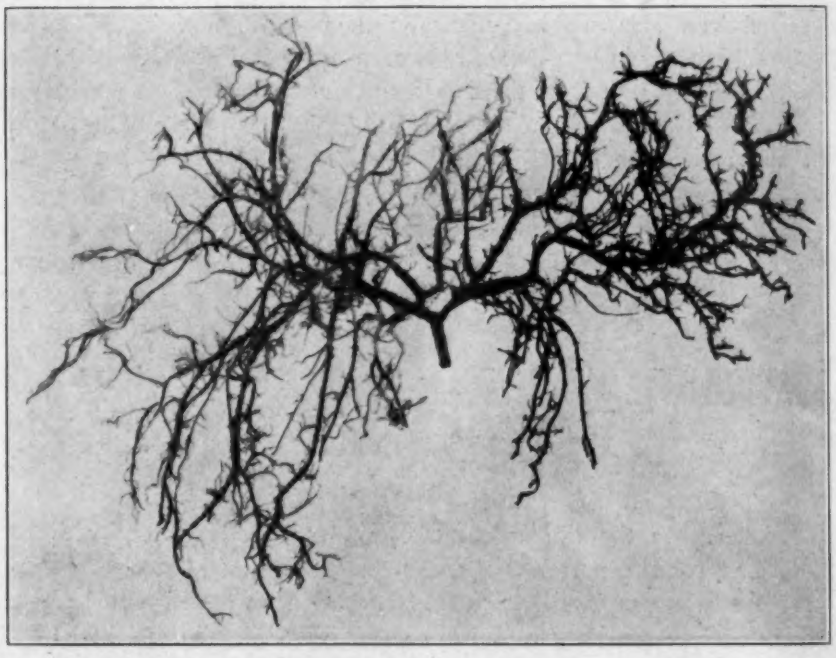

Fig. 3.—Injection of celloidin in the right and left hepatic ducts in a normal liver.

entrance of the hepatic veins into the inferior vena cava. Each half is supplied by a branch of the portal vein and hepatic artery, and drained by a branch of the bile duct. With regard to the portal vein, gross anastomosis does not occur between the two sides, only sinusoids crossing the median line. The two branches of the hepatic artery also respect the boundary line of the two lobes, but the division is not so absolute. Besides the capillary circulation, there is an arteriolar anastomosis from side to side, chiefly in the capsular and vaginal branches. The separation of the two bile ducts is absolute. While there may be an anastomosis between the bile canaliculi of the two sides, the bile ducts, per se, are entirely limited to their appropriate sides.

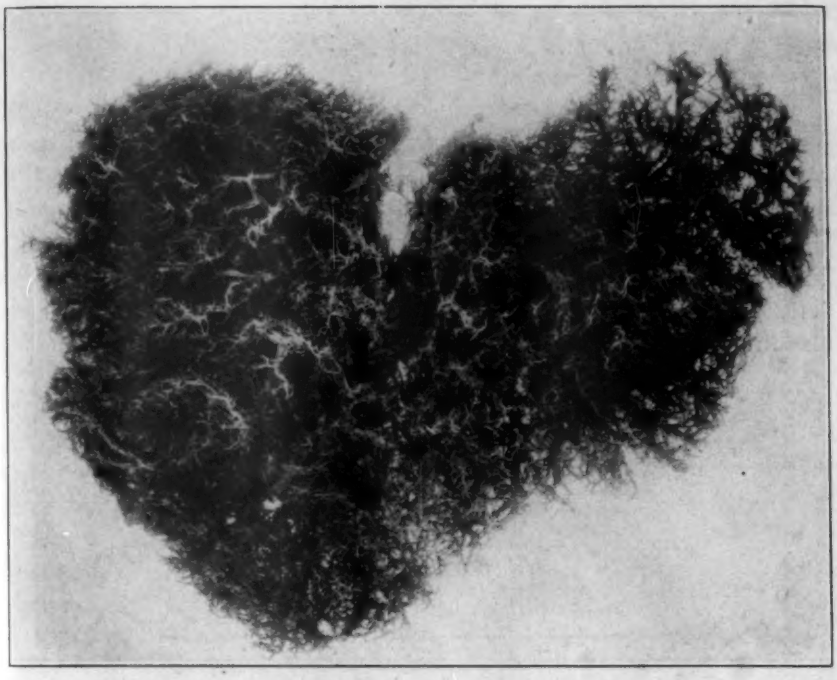

Fig. 4.—Injection of celloidin in portal vein, hepatic artery and bile ducts showing plane of separation common to all three vessels.

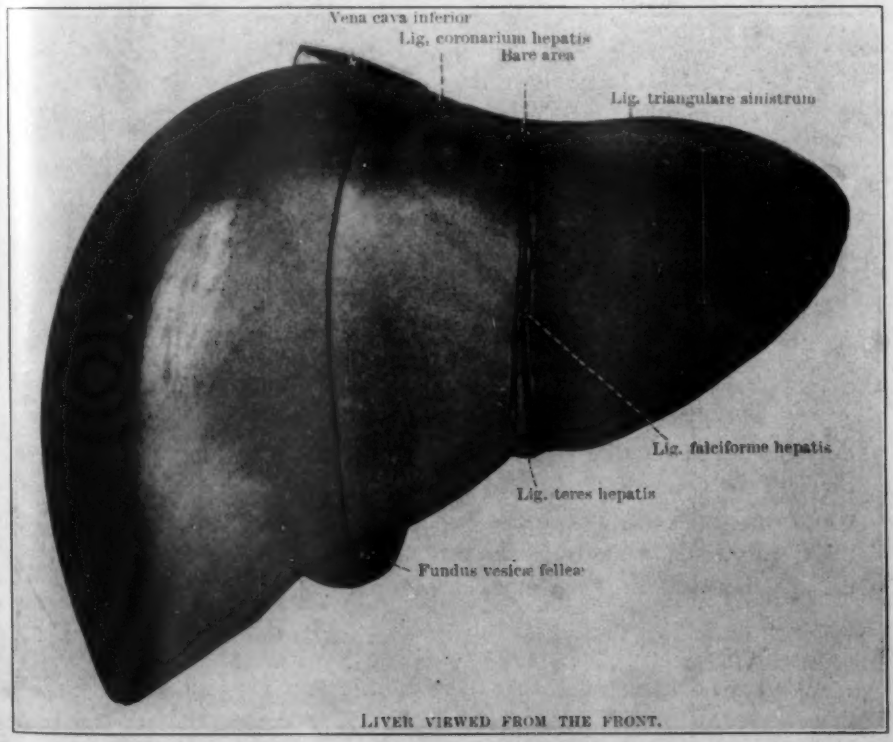

Fig. 5.—Surface markings of the plane of division; superior view (Cunningham).

SURFACE MARKINGS OF THE LOBES OF THE LIVER

The line bounding the plane of separation of the right and left lobes of the liver passes from the median point of the entrance of the hepatic veins into the inferior vena cava and straight across the superior surface of the organ to the middle of the notch for the gallbladder on the inferior margin. Occasionally there is a slight convexity to the right or left, though generally the line is direct (fig. 5). On the inferior surface the line proceeds along the middle of the fossa for the gallbladder,

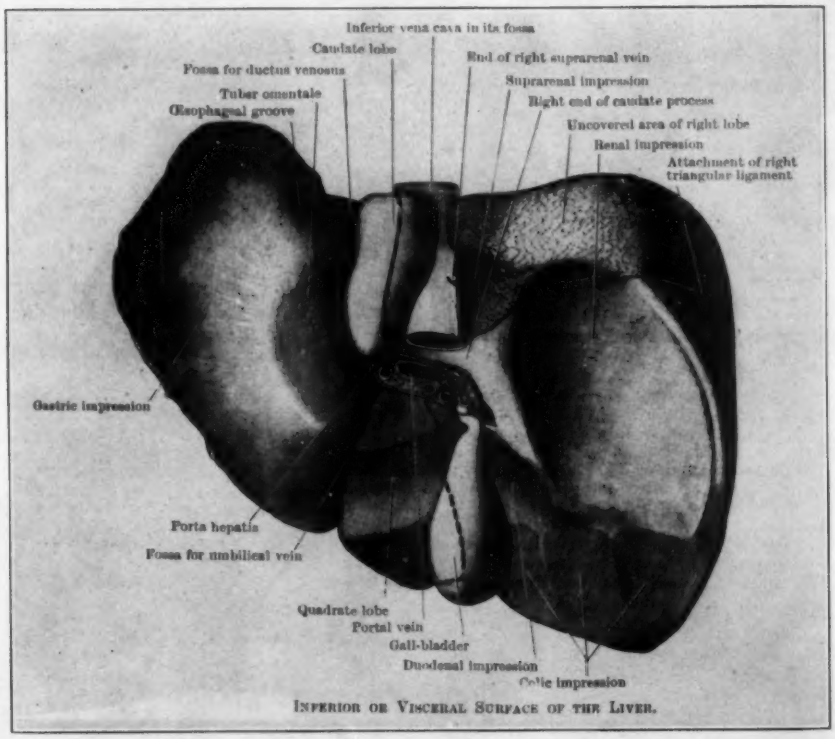

Fig. 6.—Surface markings of the plane of division; inferior view (Cunningham).

deviates a little to the left toward the porta hepatis, and then passes through the point of division of the three vessels at the hilum. It then runs toward the entrance of the hepatic veins into the inferior vena cava along the middle of the fossa for that structure, at the same time dividing the spigelian process longitudinally into halves (fig. 6).

EVIDENCE FROM PATHOLOGIC LIVERS

We have demonstrated that there is at least a constant gross separation between the two sides of the liver. How completely autonomous the lobes may be anatomically and possibly functionally will depend

largely on the efficiency of a capillary anastomosis from side to side, if it occurs. If the blood supply and biliary drainage of each lobe is entirely limited to its own side, a unilateral occlusion of the separate branches should produce a lesion involving the whole lobe, clearly marked off from the opposite side along this plane of division. On the other hand, if the circulation across the median line is free, little or no effect is produced; but if slight overlapping occurs, there is partial compensation for the lesion. The effects of such lesions are fairly well known. Occlusion of either branch of the bile duct or hepatic artery invariably leads to atrophy and cirrhosis of the corresponding half of the liver,[26] in the first case, and to necrosis in the second. As Winternitz [27] has shown, occlusion of the portal vein may or may not be followed by infarction, depending on the pressure in the hepatic artery and the presence of stasis in the inferior vena cava. As a rule, little change is noted beyond slight congestion, although massive infarcts are sometimes produced.

The following three cases were selected as being representative of what may occur in various types of unilateral obstruction in the three vessels. In each case microscopic sections were taken from various points at the edge of the resultant lesions in order to demonstrate capillary anastomosis.

REPORT OF CASES

CASE 1.—*Thrombosis of the right branch of the portal vein.*

A woman, aged 56, was admitted to the hospital with signs of pneumonia in the left side of the chest and generalized abdominal tenderness, more marked in the upper right quadrant. For five days the patient made fair progress, but following the onset of severe diarrhea, rapidly became worse, and died on the eighteenth day. At necropsy the anatomic diagnosis was adenocarcinoma of the sigmoid without metastasis, subacute hemorrhage enteritis, thrombosis of the left branch of the portal vein with hemorrhagic infarction of the left half of the liver, cloudy swelling of the liver, spleen and kidneys, and congestion and edema of the lungs.

As the interest in this case lies in the liver, a description of the organ will be given. Its weight was 1,500 Gm. Beneath the capsule on the superior surface, a sharply defined line of demarcation ran from the gallbladder notch over the dome of the organ to the region of the entrance of the hepatic veins into the inferior vena cava. The right side was composed of normal brownish-yellow

26. Behrend, M.: Experimental Ligation of the Hepatic Artery: A Preliminary Note, Surg. Gynec. Obst. **31**:182, 1920. Narath, A.: Ueber die Unterbindung der Arteria hepatica, Beitr. z. klin. Chir. **65**:504, 1909; Ueber Entstehung der anämischen Lebernekrose nach Unterbindung der Arteria hepatica und ihre Verhütung durch arterioportale Anastomose, Deutsche Ztschr. f. Chir. **135**:305, 1916. Staehlin, Edward: A Contribution to the Study of Blood Supply of the Liver, Surg. Gynec. Obst. **11**:479, 1910.

27. Winternitz, M. C.: The Effect of Occlusion of the Various Hepatic Vessels Upon the Liver, Bull. Johns Hopkins Hosp. **22**:396, 1911.

hepatic tissue, while the left presented a uniformly hemorrhagic surface, with obliterated lobular markings, and marked softening as compared with the right side. On passing the finger from one side to the other the line of demarcation was more readily perceived. After section, the right lobe appeared practically normal, except for a little swelling and indistinctness of the lobular markings. On the left side the lobules were shrunken, and almost indistinguishable, with dark red congested centers and slightly lighter peripheral zones (fig. 7). Dark blood could be freely expressed from the cut surface. The left branch of the portal vein was completely occluded by an antemortem clot which extended into several of its smaller branches. The hepatic artery on both sides and the right branch of the portal vein were free.

Microscopic examination of the right lobe showed cells apparently fairly normal in structure and arrangement. Sections from the left lobe showed almost complete atrophy of the hepatic cell columns, most marked at the centers of the

Fig. 7.—Thrombosis of the left branch of the portal vein with infarction of the left lobe of the liver. The edge of the lesion represents the true line of separation between the right and left lobes.

lobules, and slightly less in degree at the periphery. The sinusoids were hugely dilated with blood and contained many polymorphonuclear leukocytes. Sections from the edge of the lesions showed normal tissue on the right, and on the left an abrupt transition to the condition just described. It could be clearly seen, however, that many normal capillaries communicated from normal to abnormal tissue, indicating that while an anastomosis occurred, it was insufficient to compensate for the vascular occlusion on the left side. This plane of demarcation corresponded entirely to that which we have described as separating the right and left lobes of the normal liver.

CASE 2.—*Obstruction of the left hepatic duct.*

A woman, aged 56, was admitted to the Mayo Clinic complaining of intermittent attacks of severe epigastric pain radiating to the right shoulder blade and associated with nausea and vomiting of fifteen months' duration. On examina-

tion little was found except that the abdomen was tender under the right costal margin. A few days after admission, the patient became definitely jaundiced. Exploration revealed a malignant neoplasm in the region of the left hepatic duct. The patient gradually became intensely jaundiced, and died twenty-four days later. A carcinoma of the left hepatic duct was found at necropsy, with long-standing obstruction and dilatation of the ducts, marked unilateral obstructive biliary cirrhosis and atrophy of the left lobe of the liver.

At the hilum a firm, white nodular mass involved the hepatic ducts, completely obliterating the left and encroaching on the lumen of the right. The liver weighed 904 Gm. The surface of the left lobe was dark green, coarsely granular, firm, and with dilated bile ducts projecting beneath the capsule, giving the whole lobe a somewhat cystic appearance. The lobe was also atrophic, being less than 2 cm. thick. The right lobe was soft and greenish brown. Owing to the marked difference in color and consistency, the right and left lobes were clearly and definitely demarcated along a line joining the fossa for the gallbladder to the inferior vena cava. On section the left lobe was found to be tough and fibrous, and consisted of thick, dilated, unstained bile ducts filled with "white bile" and surrounded by small nodules of fibrosed and deeply bile-stained hepatic parenchyma. On the right side, the bile ducts were dilated, but their walls were thin and dark green, indicating a more recent and acute dilatation. They were filled with green bile. While the parenchyma on this side was bile-stained, there was no apparent increase in fibrous tissue, although the lobular markings were distinct. The line of separation between the two sides was situated similarly to that already described for the normal liver.

Microscopically, the left lobe showed an advanced grade of obstructive biliary cirrhosis, with tremendous increase in the periductal fibrous tissue, dilatation of the ducts and generalized fibrosis of the parenchyma. Atrophy with little attempt at regeneration was a marked feature. The right lobe showed considerable central bile stasis, but little or no increase in periductal fibrous tissue. Sections from the line of demarcation showed an absolute and abrupt transition from the one condition to the other.

It was obvious that the obstruction in the left duct had existed for many months and that jaundice had not occurred until the right duct was involved, probably not more than three weeks before death.

CASE 3.—*Obstruction of the right hepatic artery.*

While this case is not an example of a true lesion, it serves to illustrate well the effect of a unilateral obstruction of the hepatic artery. A patient who died from a pulmonary complication was embalmed several days before permission was granted for necropsy. It was then found that a small clot of blood had lodged at the origin of the right hepatic artery, effectively preventing the passage of the embalming fluid into that side. The left lobe of the liver was perfectly preserved; the right was soft and necrotic and filled with cysts, the result of postmortem infection with *Bacillus welchii*. The line of separation between the two sides was fairly definite, as could be determined by passing the finger over the surface from one side to the other. It coincided entirely with the normal plane of division of the right and left lobes.

COMMENT

As has been pointed out, it is somewhat difficult to reconcile the conflicting views of the embryologist, anthropologist and anatomist on this controversial question. It would be well, therefore, to review briefly our knowledge of the liver as pertaining to each group and to discover if

possible in how far our thesis is in harmony with them. For the facts concerning the embryology of the liver we have drawn freely from the textbooks of Keibel and Mall,[28] Bailey and Miller,[29] Kollman,[30] Hertwig,[31] Minot,[32] and Prentiss and Arey.[33] Stress has been laid on certain points since they are believed to have more importance than has hitherto been accorded them.

The liver develops as a diverticulum from the central portion of the future duodenum and invades the median sagittal portion of the septum transversum, or that part of it known as the ventral mesentery. Before mammalian embryos had been satisfactorily studied, it was known that in the chick the liver arose from two intestinal outgrowths, so that a similar development was predicted for mammals. Although a bilateral origin has been described in some invertebrates, it has not been found in man.[34] In the 4 mm. embryo the already substantial mass of liver cords is found to be growing actively into the mesenchyme of the ventral mesentery, and to be approaching the paired system of vitelline and umbilical veins which forms a remarkably constant ground-plan in this region. At this time, and coincident with the proliferating hepatic mass, the branches of the omphalomesenteric (vitelline) veins are forming plexuses within the mesentery. The result is that when the liver anlage in its dorsal course comes into contact with the vitelline veins, they invaginate one another, so that the cords of liver cells are closely invested with endothelium, and the venous channels form an intricate network of sinusoids about them (Minot). The primitive liver at this stage forms into incompletely separated halves, the right and left wings (Lewis),[35] or the right and left dorsolateral lobes (Bailey and Miller), in relation to the two vitelline veins. Thus, before the umbilical veins have become incorporated into the liver, two well recognized subdivisions have occurred in relation to the future portal vein. This is the first and only evidence of true embryologic lobes in the development of the organ.

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28. Keibel, F., and Mall, F. P.: A Manual of Human Embryology, Philadelphia, J. B. Lippincott and Company, **2**:403, 1912.

29. Bailey, F. R., and Miller, A. M.: Textbook of Embryology, ed. 4, New York, William Wood and Company, 1923, p. 316.

30. Kollman, J.: Handatlas der Entwickelungsgeschichte des Menschen, Jena, Gustav Fischer **2**: figs. 382, 383, 385, 1907.

31. Hertwig, Oscar: Handbuch der verglerchenden und experimentallen Entwickelungslehre der Wirbeltiere, Jena, Gustav Fischer **3**:139, 1906, pt. 2.

32. Minot, C. S.: A Laboratory Textbook of Embryology, Philadelphia, P. Blakiston's Son and Company, 1903, p. 100.

33. Prentiss, C. W., and Arey, L. B.: A Laboratory Manual and Textbook of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1922, p. 176.

34. Scammon, R. E.: The Development of the Elasmobranch Liver: I. The Early Development of the Liver. II. The Development of the Liver Ducts and Gallbladder, Am. J. Anat. **14**:333, 1912.

35. Lewis, F. T., quoted by Keibel and Mall (footnote 28).

In the 6.5 mm. embryo the extrahepatic portions of the two vitelline veins have anastomosed both ventrally and dorsally to the primitive duodenum to form two venous rings with three cross connections between them. By atrophy of the right side of the caudal of the two vitelline loops and the left side of the cranial one, an S-shaped course is pursued by a common vitelline trunk, composed mostly of the left vein but partly of the right, to reach the liver at the site of the former right vitelline vein. This in turn opens into the cranial anastomosis which now becomes intrahepatic. Thus the extrahepatic portion of the future portal vein is formed. Except that the liver is now supplied by a single trunk, the two intrahepatic omphalomesenteric (vitelline) plexuses retain their relationships undisturbed with the right and left dorsolateral lobes.

When the umbilical veins gain their connections with the liver sinusoids, there is a radical though temporary change in the arrangement of the venous plexuses. The right umbilical vein disappears completely early in the development. The umbilical blood is now poured into the cranial anastomosis of vitelline veins by way of the left umbilical vein, and subsequently develops a new path, the ductus venosus, to the right horn of the sinus venosus. The main factors in the formation of this pathway and its obliquity are the sudden accession in size of the right side of the liver and the consequent circuitous course taken by the right vitelline vein. Thus in the 7 mm. embryo, as has been stated, the entire right umbilical vein and caudal portion of the right vitelline are absent, leaving intact the common vitelline and intrahepatic portions of both vitellines forming the definitive portal vein, and in addition, the newly incorporated left umbilical vein. During the further development of the liver the left umbilical vein completely overshadows the vitelline. With the redirection of the blood flow obliquely across the liver from left to right, and the bulging of the organ on each side of the relatively broad attachment of the ventral mesentery to the diaphragm, the future falciform ligament, two new or secondary right and left lobes, have been generally recognized. The separation is rendered still more convenient by the fact that the falciform ligament and its contained vein, once a left lateral structure, now moves toward the median plane, while the gallbladder, which is without doubt morphologically median (Lewis), is found on the right.

At birth, however, a further series of changes occurs which obliterates all active traces of the umbilical circulation and restores the vitelline or portal vessels to their former importance. The ductus venosus and the umbilical vein become fibrous cords, and the whole blood supply of the organ is once more diverted through portal channels.

To return to the embryo of 6.5 mm., it is found that the hepatic duct consists of a single solid cord of cells joining the hepatic mass to

the common duct, and so to the duodenum. At 10 mm. it receives a right and a left branch from the right and left lobes. Within the liver the larger ducts cannot be traced far, nor is it clear whether they are outgrowths of the hepatic duct or whether they arise in situ by a transformation of the cells of the hepatic parenchyma. The smaller periportal branches do not appear until much later (22.8 mm.), and they apparently spread along the branches of the portal vein, acquiring a lumen and communicating with the parenchyma as they go. At the same time as the hepatic duct forms a single cord, the hepatic artery can be traced to it. At 22.8 mm. the artery extends along the cystic and hepatic ducts, the former branch being much larger, owing to the earlier appearance of the gallbladder. Following the development of mesenchyme around the hepatic duct and portal vein, ramifications of the artery appear within it in close association with the two vessels throughout their course. The important point with regard to both the ducts and the artery is that they are of much later development than the vein, and their disposition within the liver is embryologically determined by the arrangement of the portal vessels, and hence of the vitelline circulation.

If this account of the development of the liver is true, one should expect to find that in the adult, the right and left branches of the portal vein regularly supply the true embryologic right and left lobes of the liver, and that the bile ducts and hepatic artery agree in their distribution with the portal vein.

Our experiments show clearly that the liver of man is constantly and regularly divided into halves, according to the distribution of the portal vein, by a plane passing through the fossa for the gallbladder and the entrance of the hepatic veins into the inferior vena cava. This separation is always followed by the bile ducts and hepatic artery. It would seem, therefore, that, just as in the embryo the true plane of embryologic division is admitted to lie between the right and left omphalomesenteric veins, the only absolute and definite subdivision of the adult organ lies in this constant separation of the three vessels, the principal member of which represents the two fetal veins. The falciform ligament is of secondary importance. Under these circumstances it may be asserted with Cantlie that the liver is a bilaterally symmetrical organ, with the gallbladder as its morphologic center. The truth of this may easily be verified by sectioning the liver along the line as described and observing the total absence of portal veins, bile ducts and arteries on the two cut surfaces. Moreover, the two portions are almost equal in weight, the difference rarely being more than 100 Gm.

As the line of division between the true right and left lobes is unmarked by any fissure, unless it is by the fossa for the gallbladder and

an occasional partial or complete bifid spigelian lobe, it is necessary to explain the presence of fissures and apparent lobes on some other basis than that supplied by a single developmental cause. It is well known that in comparison with lower animals, the liver of man shows surprisingly few fissures or well marked lobulations. Comparative anatomists have noted many similarities; but, again, in such closely related species as *Gorilla gorilla,* inexplicable anomalies are found. Among the widely divergent reasons given by anthropologists for these dissimilarities are the character of the food, the configuration of the stomach and diaphragm, the position of the animal—whether erect or prone—the disposition of the fetal veins and in general the molding effect of the other abdominal organs. Harris [36] further suggests that the changes occurring in the normal physiologic umbilical hernia may yield the answer to this puzzling question. On one point the embryologist and the morphologist are agreed, namely, on the profound influence which pressure, both from intra-abdominal organs and from fetal structures, plays in the external form of the organ. Toldt and Zuckerkandl [37] have demonstrated the tremendous changes in shape which the liver undergoes from fetal to adult life. Atrophy in one situation is followed by hypertrophy in another, so that the organ is in a constant state of parenchymal movement. They attribute these changes solely to extrahepatic pressure. Definite traces of such alterations may clearly be seen in the coronary ligaments, especially on the left side, in the angle between the right and left hepatic ducts, in the transverse fissure and in the membranous bridge which unites the spigelian process with the right lobe behind the inferior vena cava. Here bile ducts, veins and arteries, preserving their hepatic relationships, are found stranded in fibrous tissue. Mall, who confirms these observations, points out that the distribution of the portal blood to the hepatic parenchyma is remarkably even, no region being especially favored, so that any enduring local irregularity would produce a shift of parenchyma. While these influences are normally constant and produce a uniformly shaped liver, the variations in form, such as have been recorded in man by Ruge and Cullen,[38] are remarkable. It is commonly known that the liver may be greatly deformed by thoracic or abdominal tumors, by collections of fluid or by external influences, such as tight lacing. More recently Rous and

36. Harris, H. A.: Intrapelvic Ectopic Testis Combined with Ectopia Vesicae, Congenital Umbilical Hernia and Abnormal Gallbladder, Arch. Surg. **13**:644 (Nov.) 1926.

37. Toldt, C., and Zuckerkandl, E.: Ueber die Form und Texturveränderungen der menschlichen Leber während des Washsthums, Sitzungsb. d. k. Akad. d. Wissensch. **72**:24, 1876.

38. Cullen, T. S.: Accessory Lobes of the Liver. An Accessory Hepatic Lobe Springing from the Surface of the Gallbladder, Arch. Surg. **11**:718 (Nov.) 1925.

Larimore [39] have shown how changes in the intrahepatic pressure relationships from local conditions may effect the shape of the organ.

The mutilobed liver of Rex, Mall and Flower, considered in relation to the smaller branches of the portal vein, is, as Bradley states, probably more of descriptive value than of morphologic significance. It is clearly absurd to dignify the slight eminence between the gallbladder and the falciform ligament as a distinct lobe, and more so to accord to it an independent blood supply. In our vascular injections we have always found that the branches named which supply these areas course along with others just as large and important, and that there is little specificity at such a distance from the portal trunk. The spigelian lobe has at least two main branches dividing it into two parts, one from each main branch of the portal vein, so that morphologically half the spigelian lobe belongs to the true right lobe and half to the left. Beyond the two principal lobes, there can therefore be little value in such minor subdivisions.

If it is admitted that the falciform ligament is a useful surgical landmark, there are certain practical objections to the assumption that it represents the line of division between the right and left lobes. These are concerned with the questions of atrophy and hypertrophy, with unilateral lesions of the liver, with the dual portal current and with the possible functional independence of the two sides. A comparison of the relative positions of the falciform ligament and the true lobar boundary will convince one that the situation of the former is by no means constant. Sometimes it is nearer to the left side; sometimes nearer to the right. An accurate estimation of the amount of atrophy or hypertrophy, or even a demonstration of its presence, may thus be impossible, unless the true dividing line between the two sides is kept in mind. On the other hand, such changes have undoubtedly been reported when in reality the liver was entirely normal. The alterations resulting from local disturbance of the portal or hepatic blood supply or of biliary drainage are analogous to the parenchymal shifting of the fetal liver. From whatever cause hypertrophy occurs, it is usually regarded as a compensatory phenomenon similar to the overgrowth of other glandular organs which occurs when they are forced to carry added functional burdens. The possibility of atrophy in one lobe essentially dependent on a similarly developing hypertrophy elsewhere does not seem to have been fully appreciated in the study of the pathologic changes of the liver. Rous and Larimore have recently shown that if the right portal vein is ligated, atrophy occurs in the right lobe with a compensatory hypertrophy of the left. If, however, the bile duct from the proliferating side is occluded and the hypertrophy checked, atrophy does not occur on the

39. Rous, Peyton; and Larimore, L. D.: Relation of the Portal Blood to Liver Maintenance, J. Exper. Med. **31**:609. 1920.

right side. Little attention has been paid to this question of conditional hypertrophy. It may well explain the advanced local atrophy found in livers containing an echinococcus cyst, a gumma, a slow growing tumor or other limited process causing pressure on portal radicles. Such portal diversion may also account for the extreme atrophy and hypertrophy met with in the so-called hepar lobatum. We have noted that, following long-continued obstruction of the common duct, there is distinct atrophy of the left lobe, due to the greater constricting effect of the dilated left bile duct on the longer and more slender left portal vein. Correspondingly, there is a more severe grade of hydrohepatosis in the left lobe. These differences are slight and can be detected only by careful observation of the relative sizes of the true right and left lobes. Microscopic examination may reveal no sign of their presence, for, as McCallum [40] has shown, large areas of hepatic tissue may disappear without the least replacement of connective tissue.

We do not intend to dwell on unilateral lesions of the liver, associated as they are with the controversial question of the dual portal current. It is sufficient that many interesting avenues for investigation are opened up. From the pathologic point of view, there is much evidence that the mesenteric and splenic circulations are destined for definite areas of the liver. The astonishing predilection of amebic abscess for the right lobe, the frequency with which parenchymatous degeneration of the same area occurs in cases of peritonitis and diseases of the intestines (Wassink) [41] and the occasional localization of metastatic carcinoma in one or the other lobe point toward this autonomy. There are at least excellent anatomic reasons why such things should occur. Whether the right and left lobes are functionally independent is another question which requires further investigation, and which is entirely beyond the scope of the present paper.

CONCLUSIONS

1. The right and left branches of the portal vein are regularly and definitely divided along a line from the fossa for the gallbladder to the entrance of the hepatic veins into the inferior vena cava. Except for the intercellular sinusoids, which are probably insufficient to maintain a collateral circulation, there is no gross anastomosis across the line of separation.

2. The right and left branches of the hepatic artery are also separated in the same manner and at the same situation. There is an arteriolar

40. McCallum, W. C.: A Textbook of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 63.

41. Wassink, W. F.: Unilateral Degeneration of the Liver Caused by Division of the Portal Circulation, Nederl. Tijdschr. v. Geneesk. 1915, p. 2145.

anastomosis between the right and left sides chiefly between the capsular and vaginal branches, but it is not sufficient to prevent infarction of the corresponding lobe following occlusion of either branch.

3. The line of separation of the right and left hepatic ducts is identical with that of the artery and vein, but the division is absolute.

4. The facts of embryology, anatomy and pathology are in accord with the assumption that the two areas of liver determined by this division, which is common to the three vessels, represent the true embryologic right and left hepatic lobes and that the falciform ligament is merely an arbitrary landmark.

SPONTANEOUS GANGRENE OF THE EXTREMITIES

DEAN LEWIS, M.D.
BALTIMORE

During the past few years lesions affecting the blood vessels of the extremities have been well differentiated and the clinical syndromes associated with them have become well recognized. It may be said, however, without much fear of contradiction, that most things concerning the etiology of the changes in the vessels leading to spontaneous gangrene and many things concerning the results of these are still in a state of distressing uncertainty.

Clinically, spontaneous gangrene occurs in the old and in the relatively young, thus justifying the clinical classification of senile and presenile gangrene. These are dependent on entirely different processes, one degenerative in character, and the other inflammatory—an arteritis or, because of the almost constantly associated involvement of veins, a thrombo-angiitis.

According to Marchand, the term arteriosclerosis includes all those changes occurring in an artery which lead to a thickening, especially of the intima; to degenerative changes (fatty degeneration); to sclerosis and calcification (including calcification of the media), and also to inflammatory and productive processes.

Clinicians and pathologists have different criteria regarding arteriosclerosis. To the clinician, arteriosclerosis indicates a rigid, noncompressible, pipestem-like artery. The pathologist, on the other hand, is concerned mostly with the earlier changes of proliferation, followed by degeneration or the reverse. It is generally admitted that in arteriosclerosis the principal changes occur in the media. In advanced cases the adventitia may also be affected. There is no unanimity of opinion, however, concerning the sequence of these changes. While some regard the changes in the media and internal elastic lamina as primary and those in the intima as secondary, others hold the opposite view. These differences of opinion may be due in part to variability in the arrangement of the musculature and elastic tissue in different parts of the arterial tree.

The changes associated with presenile gangrene are definite. There is some confusion, however, in nomenclature, because of the terms which have been introduced. In 1879, von Winiwarter published pathologic observations of cases in which practically all the arteries of the leg were obliterated by a chronic proliferative process originating apparently in the intima. He gave the name of endarteritis obliterans to this process. This lesion undoubtedly is the same as that now known

as thrombo-angiitis obliterans, characterized by an inflammation of the walls of the vessels, associated with thrombus formation, with subsequent vascularization, canalization and organization of the thrombus.

Pathologically, arteriosclerosis and thrombo-angiitis are distinct. The term endarteritis obliterans probably might be discarded to advantage. It has, however, the influence of long usage. In thrombo-angiitis, arteritis and peri-arteritis (phlebitis and periphlebitis) are the initial lesions. In the evolution of the disease, healing is the rule, the products of the inflammatory stage being replaced by fibrous tissue.

Fig. 1.—Normal pattern of the arterial tree of the foot.

In the series on which this study is based are 139 cases of spontaneous gangrene of the extremities, the records of which are complete enough to be accepted. There are forty-seven cases of arteriosclerotic gangrene, forty-three cases of arteriosclerotic gangrene associated with glycosuria, twenty-seven cases of gangrene occurring in diabetic patients in which the arterial changes, if present, were not pronounced enough to attract attention, fourteen cases of thrombo-angiitis obliterans, one case of scleroderma, and seven cases in which arterial changes may have been a contributing factor in the gangrene, but infection played the principal part.

ARTERIOSCLEROTIC GANGRENE

The clinical phenomena associated with arteriosclerotic gangrene and thrombo-angiitis are so well known that there is but little need for their consideration. I will quote, however, from the original description of Pott concerning the onset and progress of arteriosclerotic gangrene, which appeared in his "Surgery," vol. 2, published in 1819, in a chapter entitled "Observations on the Mortification of Toes and Feet." In this appears the following:

Fig. 2.—Injected specimen of leg and foot removed for arteriosclerotic gangrene showing imperfect filling of the vessels, occlusion of the main trunks and lack of collateral circulation.

The powers and virtues of Peruvian bark are known to almost every practitioner of physic and surgery. Among the many cases in which its merit is particularly and justly celebrated, are the distempers called gangrene and mortification; its general power of stopping the one, and resisting the other, has made no inconsiderable addition to the success of the chirurgic art; but still there is a particular species even of these in which this noble medicine most frequently fails. I mean that particular kind, which, beginning at the extremity of one or more small toes, does, in more or less time, pass on to the foot or ankle, sometimes to a part of the leg, and in spite of all the aid of physic or surgery most commonly destroys the patient.

It is very unlike to the mortification from inflammation, to that from external cold, from ligature or bandage, or to that which proceeds from any known cause, and this as well in its attack as in its progress. In some few instances it may make its appearance with little or no pain, but in much the majority of cases the patient feels great uneasiness through the whole foot and joint of the ankle, particularly in the night, even before there is any other than a small discolored spot on the end of one of the toes.

It generally makes its appearance on the inside or at the extremity of one of the smaller toes by a small black or bluish spot; from this spot the cuticle is always found to be detached and the skin under it of a dark red color.

Fig. 3.—Injected specimen of foot removed for arteriosclerotic gangrene; some collateral circulation seems to have developed, but it is small in amount.

If the patient has lately cut his nails or corn, it is most frequently, though very unjustly, set to the account of such operation.

Its progress in different subjects, and under different circumstances, is different; in some it is slow and long in passing from toe to toe, and from thence to the foot and ankle; in others its progress is rapid and horridly painful. It generally begins on the inside of each small toe before it is visible either on its under or upper part; and when it makes its attack on the foot, the upper part of it shows first the distempered state, by tumefaction, change in color and sometimes by

vesication, but wherever it is, one of the first marks of it is a separation or detachment of the skin.

This clinical description of senile or arteriosclerotic gangrene is so accurate that nothing can be added. The question arises at once why gangrene is not observed more frequently in the upper extremity in arteriosclerosis. Pott's original description concerns itself with the toes and feet. But in the cases of arteriosclerotic gangrene of the feet the changes may be as advanced or more so in the vessels of the upper extremity.

One must be impressed with the frequency with which pulsation cannot be felt in either the dorsalis pedis or the posterior tibial arteries and still no evidence of a circulatory disturbance be evident and no symptoms except some fatigue or pain on exertion.

The arrangement of vessels in the lower extremity may determine the more frequent occurrence of gangrene in the lower than in the upper extremity. Not enough attention has been paid to the extent or location of the thrombus or occlusion. Embolism or thrombosis of the popliteal artery is practically always followed by gangrene. Heidenhain was one of the first to suggest that gangrene of this type was due to occlusion of the popliteal arteries or its branches. In eleven of the twenty cases examined by him, occlusion of the larger vessels—popliteal, anterior and posterior tibials—by thrombi, in some cases organized, was found. An examination of statistics would indicate that in 50 per cent of the cases of senile gangrene the large vessels of the extremity are occluded. Occlusion of the popliteal artery by a recent thrombus is found in cases in which the gangrene is limited to a single toe. The possibility of a collateral circulation in these cases will be discussed after thrombo-angiitis is considered.

Nine deaths occurred in the forty-seven cases of senile gangrene, a mortality of a little over 19 per cent. Three of the patients died of pneumonia, three of embolism and two of myocarditis. The cause of death in one case is not stated. Twenty-seven patients left the hospital with wounds healed. The wounds of the remaining twenty were granulating, but they healed subsequently.

It has been impossible to follow these cases to determine the length of life after amputation for senile gangrene, for in Baltimore one deals with a floating population, in which a thorough follow-up is difficult.

In two of the cases, gangrene developed in the remaining foot, in one almost nine years after the first amputation, and in the other almost four years later. In the first of these, a recent thrombus was found in the popliteal artery when amputation was performed. This extended some distance up into the femoral artery.

Amputation through the condyles—Carden's transcondyloid amputation—is satisfactory in these cases. It is of interest to note, however, that in a considerable number of cases the incision may open after removal of the stitches, necessitating traction on the skin by adhesive strips in order to cover the stump. Death is not frequently caused by the operation, but is due to extension of the vascular disease or a terminal infection.

Fig. 4.—Foot and leg injected after removal for arteriosclerotic gangrene; vessels difficult to inject; collateral circulation not developed; recent thrombus found in popliteal artery.

ARTERIOSCLEROTIC GANGRENE WITH GLYCOSURIA (DIABETIC GANGRENE)

Since attention was first called to the not infrequent association of diabetes and gangrene by Marshall di Calvi, the relationship between the two has been studied frequently. That hyperglycemia with the associated metabolic changes is not alone the predisposing factor to gangrene has been conclusively demonstrated, for the severest form of diabetes

running a rapid course and terminating fatally, as well as the more chronic cases, with a marked hyperglycemia, may not present gangrene. It is probable that one errs as much in the opposite direction if one regards the glycosuria observed in so many of these cases as merely due to an arteriosclerosis involving the pancreatic vessels, and denies a direct etiologic relationship between the hyperglycemia and the gangrene.

Arterial changes are common in patients with diabetes. Grube found vascular changes in sixty-six of seventy-seven diabetic patients, and von

Fig. 5.—Foot and leg in case of intermittent claudication, showing arteriosclerosis of the main vessels; the dorsalis pedis and posterior tibial pulses are lacking, but this patient had no evidence of circulatory disturbance other than the intermittent claudication.

Noorden in 200 of 650 (30 per cent). Eliason and Wright have recently directed attention to this relationship. Arteriosclerosis was present in 66.6 per cent of their cases of gangrene occurring in diabetic patients. In nineteen cases it was not mentioned. Some of these cases dated back to 1903, and it was impossible to secure accurate data. They make the following statement concerning the association of the two.

Inasmuch as gangrene in diabetics occurs about five years earlier than in senile arteriosclerosis and 66.6 per cent of the cases in which the condition of the arteries was recorded, showed arteriosclerosis and 100 per cent of all pathological and x-ray examinations showed it to be present, it would appear that there cannot be any question but that the local arterial condition plays an important part in the causation of gangrene of the extremities in diabetic patients and is therefore quite analogous in this respect to the senile form of gangrene.

Accumulating evidence indicates that the so-called diabetic gangrene is due to arteriosclerosis. It is dependent primarily on the same causes as arteriosclerotic gangrene, but is complicated by hyperglycemia. The study of the series herein considered shows that gangrene develops in the diabetic patient about a decade earlier than in patients with uncomplicated arteriosclerosis. The average age at which gangrene appears in the diabetic patient is 54.4 years, while the average at which senile gangrene appears is 66.2 years. Eliason and Wright state that arteriosclerotic gangrene associated with diabetes shortens life a full decade more than arteriosclerotic gangrene alone.

In the series occurring at Johns Hopkins Hospital in diabetic patients, there were forty-three cases of gangrene with marked arterial changes, and twenty-seven cases in which arteriosclerosis was not pronounced enough to attract attention or in which no particular attention was paid to the arterial lesion. Arteriosclerosis was therefore noted in 61.4 per cent of the cases, a percentage which corrosponds closely to that of other statistics. Eighteen, or 25.7 per cent, of these patients died as the direct result of the gangrene. Death was ascribed to diabetic coma, pulmonary embolism, shock following operation in one case, lobular pneumonia, ulcerative colitis and advancing gangrene, gangrene of both feet being observed in one case.

THROMBO-ANGIITIS

Gangrene occurring in the relatively young—the presenile type—presents a different picture from that just described. It may have a variety of onsets, with intermittent claudication and symptoms referable to the deep vessels; with the appearance first of trophic changes, and an onset overlooked until the other extremity is affected. This disease is not confined to the Hebrew. One of the most striking changes in thrombo-angiitis obliterans is the extensive collateral circulation which may develop. While some collateral circulation may develop in arteriosclerosis, it is not marked. Meleney and Miller in 1925 injected the vessels of legs of Chinese which had been amputated because of gangrene associated with a vascular change in every way similar to thrombo-angiitis observed in this country. Reichert had done this two years before, but his results were not published until later. A roentgenogram of the injected vessels indicates the loss of the normal arrangement of the blood vessels, and in the main vessels patchy defects

suggesting almost complete obliteration of the lumen at some points. In stereoscopic plates, numerous arterioles may be seen which extend even to the line of gangrene.

Meleney and Miller recognized the importance of this collateral circulation, for they state that if the disease continues instead of subsiding or coming to a standstill, a contest develops between two forces: blockage of the vessels on one hand, and collateral blood vessel development on the other. There is a limit to the speed with which the collateral

Fig. 6.—Injected specimen of leg and foot removed for gangrene associated with Buerger's disease, showing the development of a rather extensive collateral circulation; the capillaries are not injected, as the injection mass does not pass into them.

circulation can develop. At present one can only guess what it is that limits the speed of the disease process, but the outcome is determined by the relative speed of the two. After an equilibrium has been established following the first attack, if a second attack comes on or a dormant process becomes active again, the contest is renewed, the margin of safety is narrower, the potential capacity of a collateral circulation is less and gangrene is more likely to develop.

It seems probable that the site of the thrombus may determine or modify the clinical course of thrombo-angiitis obliterans. A thrombus originating in the femoral artery and descending is less apt to cause gangrene than a thrombus occurring in the anterior or posterior tibial arteries and ascending to the popliteal artery.

The possibility of an extensive collateral circulation developing in such cases is indicated by the injection of vessels of amputated legs and also by the postmortem observations in cases occasionally seen in which extensive thrombosis has occurred without marked circulatory disturbances.

I will cite the following interesting case, as it indicates how extensive such a collateral circulation may be.

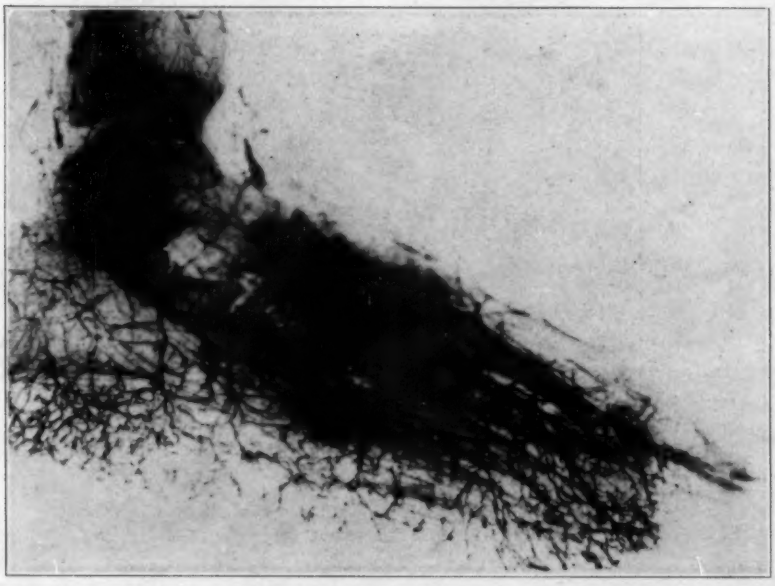


Fig. 7.—Injected specimen of foot in which amputation was done for thrombo-angiitis obliterans, showing collateral circulation; at operation a recent thrombus was found in the popliteal artery.

REPORT OF CASE

W. W., a man, aged 47, of German extraction, was admitted to Johns Hopkins Hospital, Dec. 12, 1926. About seven years before, while working at Quantico, Va., the patient noticed pains in the calves of both legs. These became worse and recurred more frequently until the summer of 1921. The condition progressed until he was unable to walk over half a block without the pain becoming so severe in both calves that he had to stop. About this time he noted that both legs would swell during the day. The swelling disappeared at night. One and one-half years later, similar pain and weakness developed in the right forearm when he worked. The pain would become so severe that he could not use his arm.

In July, 1924, an operation was performed for varicose veins. Multiple incisions were made on both sides, and sections of the veins were removed. The intermittent limping still persisted.

Physical examination revealed the man to be well developed and well nourished. The heart sounds were faint, a slight blowing systolic murmur being heard at the apex. The radial pulse was not palpable on the right side. The left radial pulse could hardly be felt; but the arteries were not like pipe stems. Scars of previous operations could be seen on the legs. Both feet were flushed. Pulses in the dorsalis pedis and posterior tibial arteries could not be felt, but the arteries did not seem to be sclerotic. When the legs were placed over the side of the bed, the feet became bluish red and engorged. This discoloration persisted for several minutes when the lower extremities were placed on the level. The feet felt cold.

Fig. 8.—Injected specimen of foot shown in figure 7, which demonstrates that the collateral vessels which are formed developed well up to the line of gangrene.

The hands were red, but blanched quickly when pressure was applied. Palpation of the brachial arteries failed to reveal any pulse on the right side; there was but a slight pulse on the left side. The carotid pulses were obtained with difficulty. Palpation of the femoral pulse was difficult because of the overlying fat.

Blood pressure readings could not be obtained in the right arm. On the left side the pressure was 136 systolic and 90 diastolic. It was suggested that the left femoral artery be tied. This was done. During the night the patient became hemiplegic and died.

I will quote at some length the pathologic observations, because they indicate how extensive arterial occlusion may be, without marked functional disturbance.

The following paragraphs are taken from the autopsy record:

The most interesting condition in the autopsy and that which appeared to be of the greatest significance was found in connection with the general arterial tree.

At the level of the celiac axis the aorta suddenly became reduced in diameter so that it measured hardly more than 1 cm. There was an old organized thrombus which totally occluded the abdominal aorta beginning at the level of the celiac axis and extending all the way to the bifurcation. From about 5 to 8 cm. below the celiac axis there was a small, crescent shaped channel which was the only

Fig. 9.—Histologic specimen of the lft common iliac in cases cited in the text, showing multiple thrmboses occurring apparently in a diffuse thrmbo-angiitis obliterans; the clinical history of the case would indicate that an extensive collateral circulation must have developed.

channel which passed through this portion of the aorta. When a probe was passed through the channel from above downward it was found to end about 5 cm. above the bifurcation, where it communicated directly with a comparatively large branch which left the aorta and spread out into the surrounding tissue. Below this branch there was no lumen within the aorta. It was totally blocked by an old organized thrombus which presented on section a peculiar transparent appearance. A complete blockage of the celiac axis had resulted from a comparatively fresh thrombus which extended from the celiac axis into the lumen

of the aorta or perhaps in the opposite direction. The portion of the thrombus which was in the lumen of the aorta communicated with the fresh thrombus which lay between the exit of the celiac axis and the organized thrombus which filled the abdominal portion of the aorta. The beginnings of the common iliac arteries were occluded by old organized thrombi which had many channels. The thrombosis affected the internal and external iliacs on both sides. The left external iliac, just before it became the femoral was only partially occluded by a thrombus. This was also true of the right external iliac. In the femoral artery on the left side extensive thrombotic changes were seen. None of the branches of the femoral group appeared normal.

In the right femoral region there were extensive thromboses of the femoral artery and its branches. All the main branches of the arch of the aorta showed sclerotic changes. Total occlusion of the second portion of the right subclavian was found, this extended into the axillary and brachial arteries. The right external carotid was closed by a thrombus. The point of origin from the common carotid was represented by a puckered scar. About 2.5 cm. above the bifurcation of the common carotid the internal carotid artery was found plugged by an organized thrombus through which passed small, newly developed channels. Proceeding upward into the skull a similar thrombotic process was found in the internal carotid at the point of anastomosis with the vessels from the opposite side.

This extensive process, going on apparently for years, must have been accompanied by an extensive collateral circulation; otherwise gangrene or death of tissues would have resulted.

I have quoted from this record merely to indicate how extensive thrombosis may be and still function be maintained by a collateral circulation.

There is definite evidence in cases of thrombo-angiitis that gangrene in many cases is due to the extension of the process to the popliteal artery. Recent thrombi are not infrequently found in this vessel when an amputation is performed.

The indication in the treatment would seem to be to force the collateral circulation ahead of the advancing thrombus. Ligation of the femoral artery has been performed in seven cases; in four there has been a distinct improvement. In two cases ligation has been performed after gangrene had developed; subsequently amputation was necessary. In one case death followed the operation. Death resulted from hemiplegia thirty-six hours after the operation. In another case an infection was present and ligation was not attempted.

CONTROL OF PAIN

Pain in thrombo-angiitis undoubtedly is due to a number of different factors. It may be a true arterial pain. In four cases the pain has been controlled. The operation puts at rest an inflamed artery. Its final result will depend on whether or not the collaterals which develop are diseased. An attempt is now being made to determine this.

That a collateral circulation does develop is also indicated by the frequency with which amputations through the middle of the leg are

successful in thrombo-angiitis obliterans. The high percentage of failure in this type of amputation in arteriosclerotic gangrene indicates a difference.

In the treatment of so-called diabetic gangrene there must be the closest cooperation between the surgeon and the internist. Insulin has changed the outlook and has practically done away with that most distressing accompaniment of surgery, diabetic coma. Inflammatory processes increase the normal blood sugar. They produce the same effect, but to a great extent in the diabetic patient. Particularly in the case in which an infection has developed, cooperation should be the closest, for often it must be decided whether an operation should be performed in the presence of a marked hyperglycemia, because it is impossible to control it in the presence of infection; or whether it is best first to institute antidiabetic treatment with the hope of improving the patient's condition. Insulin has robbed diabetes of its distressing surgical complications. It cannot be expected to aid much in limiting the gangrene, for this is caused by the same mechanism as gangrene in the senile arteriosclerotic patient, the occlusion taking place at much the same level.

Either a transcondyloid or a Gritti-Stokes amputation is the best.

In thrombo-angiitis one is dealing with another process in which the development of a collateral circulation is a striking feature. One can attempt to keep the collateral circulation ahead of the advancing thrombus by ligating the femoral artery below the profunda, or, if amputation is necessary, the collateral circulation may be sufficient to permit an amputation through the leg. The development and behavior of the collateral circulation determines the line of procedure.

SUPRARENAL HEMORRHAGE

CHARLES E. FARR, M.D.
AND
KURT SEMSROTH, M.D.
NEW YORK

REPORT OF A CASE

History.—J. C., aged 34, an Italian, married, salesman, entered the New York Hospital, First Surgical, or Cornell, Division, in the service of Dr. Gibson, Jan. 25, 1925. His chief complaint was pain in the right side of the abdomen of two weeks' duration. Two weeks before entering the hospital he began to have dull pains in the abdomen in the epigastric region. They were not severe, and he continued to work until four days before admission to the hospital. At this time there was a sudden onset of sharp pain in the epigastrium, and he became faint. His bowels had not moved, and he took an enema. Soon after its introduction there was another sharp pain in the epigastrium, quickly shifting to the right hypochondrium. The pain was somewhat relieved by the enema, but later became so severe that he called a physician, who gave him two hypodermic injections, which did not give relief. His condition steadily progressed, and the pain was constant in the right side. He had some fever, but did not vomit at any time. The abdomen became distended, but this condition was relieved by the enema. The past history was entirely negative, so far as he knew. He had always been an able-bodied, robust, hard-working man. The family history also was negative, to the best of his knowledge.

Physical Examination.—This revealed a well nourished, well developed man, slightly anemic and evidently acutely ill. Results of a thorough physical examination, including a neurologic examination, were negative, except for the abdominal observations and slightly inflamed tonsils. The man was of large build, bordering on the obese.

The abdomen was distended, tender and rigid. In the right lower quadrant and throughout the right side, there was a sensation of a mass lying in the right iliac fossa and extending upward in front of the kidney. It was approximately 15 cm. in width, and perhaps 25 cm. in length. It appeared 5 cm. thick, and was retroperitoneal. The remainder of the abdomen was tympanitic and slightly tender. Rectal examination revealed a tender mass in the right pelvis.

The urinalysis was negative for blood, pus and albumin. Examination of the blood showed 2,880,000 erythrocytes, with 35 per cent hemoglobin, 28,000 leukocytes, 86 per cent polymorphonuclear leukocytes and 14 per cent lymphocytes. His temperature on admission was 102 F., the pulse rate was 128, and the respiration was 32. The tentative diagnosis was appendicitis with abscess, or possibly a perinephritic abscess. Neither diagnosis was completely satisfactory and an exploratory operation was decided on.

Operation and Course.—A right rectus incision was made under nitrous oxide ether sequence, and the peritoneum was opened. A moderate amount of blood-stained serum with a few clots was found free in the peritoneum. A large mass of omentum appeared in the wound, and was pushed aside with pads. The entire ascending colon and the right half of the transverse colon and mesocolon were found to be the site of an enormous massive hemorrhage with old

and recent clots and some active bleeding when the mesocolon was split. The appearance was not unlike that of an extensive old necrotic hypernephroma. The right kidney was readily located, lifted from its bed and shelled out of its fatty capsule. Both seemed normal except for the extensive hemorrhage present everywhere. The kidney was replaced. Further exploration showed the hemorrhagic mass extending all along the vena cava inferior to the diaphragm, and downward into the true pelvis. A transverse incision through the right rectus outward to the quadratus lumborum gave excellent exposure, and a rapid but rather careful examination of all the abdominal organs did not reveal anything abnormal. Close attention was paid to the liver, spleen, gallbladder, stomach, duodenum, colon and appendix. The colon was freed by incising the peritoneum along the outer border, and large masses of clots were removed. Huge clots were present everywhere, in places well organized and apparently several days old. There seemed to be active bleeding, but arteries actually spurting could not be seen. The wound was packed firmly with two large Gibson Mikulicz tampons, and was partly closed with silkworm gut figure-of-eight sutures. The operation required thirty-five minutes.

The patient's condition became steadily worse during the operation. Two hours later, a hypodermoclysis of 1,000 cc. was given. He received three hypodermic injections of morphine, one-fourth grain (0.16 Gm.) each, also caffein sodium benzoate, hypodermically. At 8 o'clock the next morning his temperature had risen to 103 F., his pulse rate had fallen to 120, and his respirations were up to 56. He died rather suddenly at 8:20 o'clock without any special symptoms.

The house surgeon's discharge note mentions an indefinite history of three weeks with pains in the arms and legs. He was uncomfortable, but kept at work until four days previous to admission. He then felt a sensation of mass in the epigastrium and moderate pain. After the enema there was a sensation of something giving way suddenly in the epigastrium and a shifting of the pain to the right side, with a feeling of weakness. After this another enema gave relief, but the pain persisted in the right side, and two days before admission it became so severe that he had to have hypodermic injections. He never vomited and never felt nauseated. He was markedly distended with gas. On admission he complained of pain in the right side of the abdomen with a palpable, tender, firm mass occupying almost the entire right half.

At operation the abdomen was found filled with free old blood, and there was a large old retroperitoneal blood clot. A hypernephroma was suspected but the right kidney was explored and found normal. The source of bleeding was not found. The condition became unfavorable on the operating table. Saline infusion and hypodermoclysis restored good quality to the pulse. This lasted until 6 o'clock the next morning, when there was a sudden change for the worse. He died at 8:20 a. m.

Autopsy.—Autopsy was performed by Dr. Semsroth, at 1:30 p. m. The diagnosis was: adhesive bilateral pleurisy, fat infiltration of the liver, hemorrhage of the head of the pancreas, haemoperitoneum, extravasation of blood in the retroperitoneal space, chronic splenitis, old infarct(?) of the left kidney, chronic bilateral nephritis and suprarenal apoplexy on the base of infection.

The body was that of a well developed and well nourished white man. The skin was extremely pale, the hair black and normal in distribution. On the right side of the abdomen was a "T"-shaped surgical incision about 12 or 15 cm. in length. The lateral angle of the horizontal incision was not closed,

and several rubber drains had been introduced through this opening into the retrocecal space. The surgical incision was opened and prolonged upward to the upper edge of the manubrium sterni. The retroperitoneal surface of the colon ascendens was covered with a rather firm blood clot measuring about 10 cm. in length. The peritoneal cavity contained a considerable amount of free blood. Both pleural cavities showed a good many old fibrous adhesions between both leaves of the pleura, most pronounced at the facies diaphragmatica of both lungs.

The right lung weighed 500 Gm., the left, 300 Gm. Both organs were crepitant throughout and failed to show gross lesions.

The heart weighed 500 Gm. The myocardium was fairly pale brownish red but did not show focal lesions. The edge of the mitral valve showed a few old thickenings. All other valves were intact. The ascending arch of the aorta showed a moderate amount of arteriosclerotic change. There were a few yellowish spots on the endocardium of the left ventricle near the aortic valve. The mitral valve measured 10 cm.; the aortic valve, 6 cm.; the tricuspid, 11 cm., and the pulmonary valve, 8 cm. The thoracic aorta showed a slight amount of arteriosclerotic change.

The spleen was enlarged and weighed 300 Gm. The surface was grayish blue, but the cut surface was brownish red. The normal markings were rather cloudy. The pulp scraped easily.

The gastro-intestinal tract did not show gross lesions.

Part of the body of the pancreas was pushed aside by a cavity filled with a blood clot measuring about 5 cm. in diameter. This cavity showed a free opening into the bursa omentalis. The bursa omentalis contained a large blood clot about 8 cm. in diameter. The blood clot was separated from the tissue of the pancreas by a rather hard, yellowish-white wall. Owing to the fact that most of the surrounding tissue showed an extreme bloody imbibation, a connection of the cavity with an adjacent artery was not found. Arising from this blood cavity a long mass of firm blood clot extended down into the retroperitoneal tissue, on the left side of the spine. The inferior vena cava was intact. The mesentery showed a considerable extravasation of blood near its root. The larger part of the pancreas, especially the tail, failed to show gross lesions.

The liver weighed 2,050 Gm., was about normal in size and showed a good deal of fat infiltration. The gallbladder was normal in appearance.

The right kidney weighed 150 Gm.; the left, 150 Gm. Both were enlarged. The capsule stripped easily. Section showed a patchy appearance, in parts grayish red, in other parts yellowish gray. The left kidney showed at one side large irregular thickenings. Section of this part showed that the cortex was narrow and cloudy. The pelvis and ureters failed to show gross lesions. The bladder and internal genitalia appeared normal. The abdominal aorta contained a postmortem blood clot. There was only a slight amount of arteriosclerotic change. The lymph nodes did not show gross lesions.

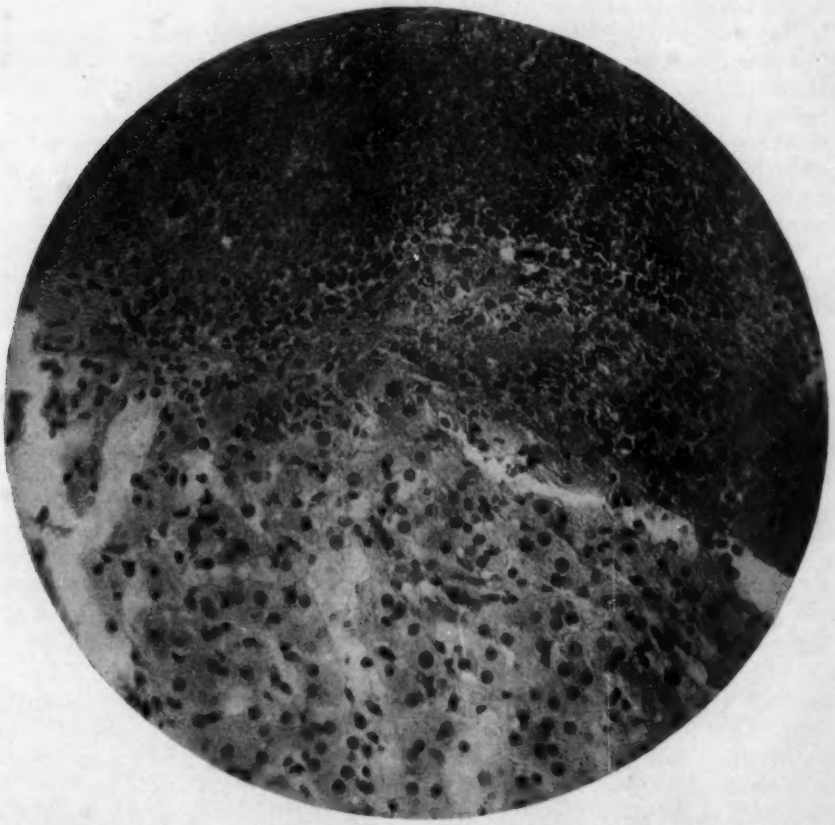
The suprarenals were not found. A specimen of abdominal viscera was fixed, to be examined carefully later.

The pancreas with the surrounding structures, was fixed in formaldehyde. On cross-section of the blood clot near the inferior vena cava the suprarenal cortex was found embedded in the clot. The cortex did not form a closed ring around the medulla, but the space normally occupied by the latter opened widely into the surrounding blood masses. The medulla could not be recognized, but it was replaced by a hemorrhage which showed a widely open direct connection

with the large retroperitoneal extravasations of blood. The suprarenal cortex itself was yellowish-white, and contained some brownish strands arising from the reticular layer. The portion of the splenic artery running on top of the pancreatic body was found intact, so that the first tentative diagnosis of ruptured splenic artery had to be rejected.

There was apoplexy of the right suprarenal medulla.

Microscopic Examination.—There was a considerable amount of engorgement of the vessels of the lungs. The interalveolar capillaries at many places were



Suprarenal hemorrhage, showing extravasation of blood and diffuse infiltration with polymorphonuclear leukocytes, more dense at the borderline between the cortex and the medulla.

tortuous, protruding into the alveolar lumen. Many alveoli contained accumulations of desquamated epithelial cells. These desquamated cells contained a great many brownish-black minute granules varying in size and shape. These granules were likely to be blood pigment hemosiderin and were characteristic for high intrapulmonary blood pressure. The accumulations of cells loaded with pigment were most numerous near the pleural surface. At several places these cells were within the interstitial connective tissue and at some places also in the bronchial lumina. The interstitial connective tissue showed some accu-

mulations of mononuclear round cells, especially around some bronchi. There was moderate anthracosis. The pleura was thickened and showed some fibrinous coverings.

The muscular fibers of the myocardium at many places showed accumulations of yellowish brown pigment granules. These accumulations were spindle-shaped and were situated around the nucleus, the typical appearance and site of lipofuchsin granules. In the interfibrillar connective tissue, especially around some vessels, were small accumulations of large cells. These cells did not show any regular arrangement. Some of them had a large, faintly stained nucleus, and some resembled lymphocytes.

The capillary vessels of the central parts of the lobules of the liver were engorged and dilated; the columns of liver cells appeared to be narrow. The cells of these parts often contained accumulations of small yellowish-brown pigment granules. On the other hand, the parenchyma cells of the peripheral parts of the lobules were swollen. They showed a cloudy granular appearance and the borderline of the cells were often indistinct. The periportal connective tissue showed a moderate round cell infiltration.

Passive hyperemia was present.

The number of pulp cells in the spleen was increased, and there was a moderate hyperemia. The number of trabeculae also appeared to be increased.

The renal epithelium showed an advanced parenchymatous degeneration. Some tubules contained hyaline casts, the intercapsular space of Bowman's capsule contained often mostly roundish red-stained homogeneous masses. The area showing in the gross thickening of the surface consisted of a uniform looking tissue. Here there was a considerable increase of the interstitial connective tissue. Scattered through this were many narrow tubules. These tubules were lined by a dense epithelium consisting of fairly small cells with large, deeply-stained nuclei and bluish stained protoplasm. These cells had at many places lost their connection, and many of them were desquamated. They differed distinctly from those of the parenchyma by their smaller size, the bluish staining of the protoplasm and their dense arrangement. The glomeruli of these parts appeared intact; the interstitial tissue showed a diffuse cell infiltration. This area showed a sharp border against the parts just described. The medulla showed a considerable increase of interstitial connective tissue. At several places the area of a medullary ray was occupied by the same kind of lesion as that described, with numerous narrow tubules lined by a dense bluish stained epithelium. The vessels of these appeared engorged.

At many places the cortical epithelium of the suprarenal had a spongy appearance. In some parts there were extravasations of blood and diffuse infiltration with polymorphonuclear leukocytes, especially in the reticular layer. At the borderline between the cortex and the medulla there were dense accumulations of polymorphonuclear leukocytes. The medulla was destroyed, and was replaced by extravasated blood. The latter showed at several places distinct lamination; narrow strands of fibrin were at both sides, covered with dense accumulations of leukocytes. These strands were situated between large accumulations of erythrocytes, so that the appearance of a thrombus resulted. At a few places the medulla appeared intact.

The diagnosis was suprarenal apoplexy on the base of infection.

REVIEW OF THE LITERATURE

Hemorrhages into the suprarenal gland are not uncommon. Indeed, if one includes cases of marked congestion of the suprarenal with tiny hemorrhages in the medulla, the condition is extremely common. Small

focal necroses are also found fairly frequently. True abscesses are not so common, but have been mentioned in the literature.

The first mention of suprarenal hemorrhage was by Moissenet and Rayer, and again by Rayer in 1837. This was followed by Valleix in 1838. The condition was not mentioned again until Mattei's report in 1863, and that of Guemot in 1865. Hervey and Ahlfeld each reported cases in 1870.

In 1902 Simmonds described suprarenal hemorrhage at great length. He stated that the condition was common in the cortex, and that it usually followed acute infectious diseases, such as diphtheria, pneumonia, typhoid, osteomyelitis and sepsis. It is probably toxic, as great amounts of bacteria are not found in the lesions. Gross bleeding is rare, but infarction, hematoma and blood cysts are occasionally seen. Symptoms may not be present, and yet the outcome may be fatal. In some cases there are convulsions and signs of peritonitis. Cases giving the picture of Addison's disease in the terminal stage have been described. Simmonds had seen only one death caused by actual hemorrhage. The patient was a man, aged 57, with sudden epigastric pain radiating to the back, followed by vomiting. The diagnosis of peritonitis was entertained. He died two days later. Autopsy showed recent bronchial pneumonia and hemorrhagic infiltration of both suprarenals. Thrombi were found in the veins of both, but inflammatory signs and micro-organisms were not present.

Simmonds considers that many extensive bilateral hemorrhages should be regarded as antemortem and without symptoms or significance. He reports a second case in a man, aged 53, with varicose ulcers and chronic heart disease, complicated by nephritis and embolism of the superior mesenteric artery. He found hemorrhagic infarcts of both suprarenals, probably secondary and not the cause of the peritoneal symptoms. He states that unilateral hemorrhage may cause large tumors with grave symptoms, and that occasionally surgical intervention is necessary. Few cases have been noted in the literature. He quotes Pawlik, who reported the death of a woman 40 years of age. The abdominal cavity contained 10 liters of old blood clots. He mentions a case of Chiari, who reported a blood tumor which weighed 6 kilograms. There was no neoplasm, but there were bleeding and calcarious concretions in one suprarenal.

Simmonds considers the etiology as variable. Trauma is the cause in certain cases, and even the destruction of the suprarenal vessel may follow contusion (Wallman). Hemorrhage in the suprarenal of the new-born is common. If the child lives, the hemorrhage is resorbed. It is seldom seen in later infancy. He has never seen large hematoma of the new-born. He quotes Ahlfeld, who had a patient who presented a bilateral hematoma the size of a hen's egg. Another case is described

by Fiedler, in which a 4 day old infant presented a clot the size of a hen's egg in the right suprarenal, which had perforated into the peritoneal cavity. He considers thrombosis of the suprarenal veins as the most common cause. He has had seven cases of this type. Hemorrhage, or infarct, will follow, according to the mechanical condition of the vessels. The blood stream is slow. The right suprarenal is more often involved than the left. Gross degeneration of the suprarenal is not present, except as a result of the bleeding. The intact organ of the pair does not show degeneration. Fatty infiltration is normal.

Simmonds also reports four cases of capillary bacterial emboli with hemorrhage. He thinks that gross hemorrhages are probably due to the local effect of the bacteria, whereas smaller ones are toxic. In the lesser hemorrhages recovery ensues with hyperplasia of the opposite suprarenal.

An extensive literature has developed on the subject of suprarenal hemorrhage, but fairly close study of the cases has failed as yet to reveal one in which a patient who received surgical treatment recovered. The difficulties of diagnosis are extreme. The lesser hemorrhages do not require surgical treatment. The gross hemorrhages might be relieved by operative removal of the suprarenal or by tamponing the area of the hemorrhage. This was attempted in the present instance, although an accurate diagnosis had not been made.

Hemorrhage into the suprarenal of the new-born is fairly common. Dr. J. R. Losee, in a personal communication, states that in 196 stillbirths and new-born babies in 1924, he found nine cases of suprarenal hemorrhage. Among 219 autopsies in 1925 there were twelve cases of suprarenal hemorrhage. The hemorrhage had not passed the capsule, although in some patients the capsule was much distended. He has not seen a case in an adult. As to the relation between suprarenal hemorrhage and death in the new-born, Dr. Losee states that he feels sure of one death from suprarenal hemorrhage. This was bilateral. The infant had convulsions, muscle spasm and other symptoms which are otherwise considered evidence of cerebral hemorrhage, but the anterior fontanel did not show tenseness. At autopsy a hemorrhage was not found in the brain, but there was extensive hemorrhage in both suprarenals. He quotes a personal conversation with an obstetrician in a neighboring city who had a case with exactly similar history and autopsy observations.

It is Dr. Losee's opinion that with extensive hemorrhage in the suprarenal, the cortical cells are destroyed rather early, and that conservative treatment is indicated rather than surgical procedure. He does believe, however, that hemorrhages of definite macroscopic size are pathologic and not physiologic. The data he quotes are from the Lying-In Hospital Pathological Laboratory.

CONCLUSIONS

Hemorrhage into the suprarenal is a fairly common condition. It is possible that some hemorrhages of minute quantity are not abnormal. Probably many occur shortly antemortem, and are not of significance in themselves.

Suprarenal hemorrhages may be unilateral or bilateral, of large or small size, confined to the capsule or spreading into the retroperitoneal tissue, or even into the peritoneal cavity. Spontaneous recovery undoubtedly occurs. Diagnosis of this condition is extremely difficult, and it is doubtful whether it can ever be definitely made ante mortem.

Massive hemorrhages which result in large collections of blood may at times be palpated, and they are suitable for surgical procedure, if the diagnosis can be established.

RELATION OF NITROGEN BODIES OF THE BLOOD TO SURGICAL PROBLEMS IN LIVER AND IN BILIARY TRACT DISEASE

III. STATUS OF NITROGEN BODIES OF BLOOD IN SEVERE CASES OF BILIARY TRACT DISEASE AND ITS USE IN DIFFERENTIATING A TERMINAL HEPATIC AND A TERMINAL RENAL GROUP OF CASES *

ABRAHAM O. WILENSKY, M.D.
AND
RALPH COLP, M.D.
NEW YORK

In the preceding papers of this series, it was pointed out that the results obtained in the clinical study of the nitrogen metabolism and especially of the status of the urea, nonprotein nitrogen, uric acid and creatinine of the blood in biliary tract conditions, established the principle that under such conditions individual figures meant little, if anything, and that it was permissible to base judgments only on major movements observable in comparable series of cases.

In the ordinarily mild, or moderately severe, case of biliary tract disease, as shown in the series studied, disturbances of nitrogen metabolism leading to retention of nitrogen bodies in the blood, were, as a general rule, not recognizable in clinical practice before operative intervention was undertaken. It was not possible to correlate any of the changes observable in the milder form of disease with similar conditions which could, and have been, more completely produced artificially in the experimental laboratory—at least, as far as their relation with the observable changes in the blood chemistry was concerned. This was not interpreted to mean that no such changes existed; rather, perhaps, that in clinical practice these abnormalities might exist, but that owing to their slight extent, or to the enormous compensatory efforts of the organs of the body, notably of the liver and the kidney, the changes do not assume sufficient dominance to make themselves perceptible or prominent in the clinical picture.

Owing to the nature of the ailment and to the fact that patients with biliary tract disease frequently are not operated on or even are not treated until the essential lesion is relatively far advanced, complicating factors—especially jaundice and nephritis (renal epithelium degeneration)—are frequently present at the time of observation, either indi-

* From the Mount Sinai Hospital, New York.

vidually or together. In the cases of the series reported in the previous communications, the jaundice was usually mild and temporary, and the nephritis was symptomless and for the most part a "laboratory" phenomenon. In the milder forms of biliary tract disease no differences could be noted, as far as the nitrogen bodies of the blood were concerned, between the uncomplicated cases and those in which these milder forms of jaundice and of nephritis were present.

In a considerable percentage of the cases, changes in the nitrogen bodies of the blood were demonstrable after operative intervention. In a general way, the relationship of the ante-operative to the postoperative observations could be classified in the following three groups:

1. A group in which the preoperative and postoperative status was practically identical.

2. A group in which the postoperative status showed a regression from the preoperative status.

3. A group in which the postoperative figures showed a progression from the preoperative status.

All that one is permitted to say in regard to the cases in the first group—with comparatively identical preoperative and postoperative figures—is that the net result of whatever has happened pari passu with the operation and during the convalescence, as a consequence of any factor associated with either the original disease or the operation, has been insufficient to disturb the status existing before operation. Such cases are not necessarily restricted to the group in which the operation is not followed by any complication, i. e., jaundice or nephritis, or both. To a smaller extent, cases were observed in which jaundice or nephritis appeared after operation, and under such conditions it seemed fair to assume, not that changes did not occur, but that their perceptible effects were rectified by the compensatory mechanisms.

The cases in the second group—those with postoperative regression from the preoperative status—are extremely interesting. From preoperative observations alone, it had been assumed prior to operation that the figures obtained were "normal." In the light of the consistent diminution in the figures that occurred in this group after operation, it seemed more correct to say that the preoperative status is "abnormal," and that the postoperative change indicates an improvement in the condition. This illustrates the importance of not making judgments based on any individual observation—a fact to which we have referred several times. The regressive changes of the second group were observed most often in cases of long standing and in uncomplicated cases as well as in cases associated with nephritis or jaundice.

The third group—cases in which there was postoperative progression from the preoperative status—are important from a clinical standpoint. The dominant fact is that something had occurred, either during or following the operation, which changed the preoperative status. This change has been observed in uncomplicated cases i. e., in cases accompanied by jaundice or nephritis.

The present communication takes up the study of the severe types of biliary tract disease at this point. Our purpose is, first, to describe the clinical phenomena as the essential pathologic, and its consequent hepatic and distant renal, complications develop into the severe type of lesion discussed in this communication; secondly, to correlate the laboratory observations with the observable clinical phenomena; thirdly, to show that the presence or absence of retention of nitrogen in the blood retention divides cases of essential biliary tract lesion into a terminal hepatic and a terminal renal group of cases; and, finally, to trace the complete development of this biologic entity.

CLINICAL OBSERVATIONS

The severe type of biliary tract disease, while presenting essentially the usual symptom complex seen in mild or moderately severe cases, becomes demarcated from the latter, however, by certain observable subjective and objective phenomena. These are always to be interpreted as indicating a progression of the effects of the pathologic changes into potential or established comparatively late stages of physiologic disturbance. In this regard, the element of time seems to have no importance. The subjective factors that indicate the change from a mild, or moderately severe, type of disease to the more severe type studied in this communication, include the following:

1. The severity of the general symptoms, especially of fever and chills. This item is the least important in judging the gravity of the case from the point of view from which we are studying it.

2. Anorexia and vomiting. These symptoms are constantly present in all types of cases. However, when they persist beyond the initial stage of the disease or exist in an aggravated form, they indicate disturbances in function bordering on, or frankly associated with, states of toxemia, the various grades of which will be commented on.

The observable objective phenomena associated with severe types of biliary tract disease include the following:

1. Shrinking in the size of the liver. This does not mean the shrinking of a swollen and enlarged liver to its normal size and proportions. When the evidences of shrinkage are reliable and indicate a decrease below the normal proportions of the liver, this shrinking becomes the most important single clinical indication of destruction of parenchyma of the liver; the signs of disturbance of liver

function follow quickly and to an equal extent and may ultimately become of extreme grade, even progressing to a terminal toxemia. The ultimate stage of such liver shrinkage is found in acute yellow atrophy of the liver. Leucin and tyrosin are then frequently found in the urine.

2. A sudden and large diminution in the discharge of bile from an external biliary fistula after operative relief of an obstruction and in the absence of any further obstruction when the amounts of bile simultaneously discharged into the intestinal tract remain constant as evidenced by stool examination. This never occurs unless there is marked interference with the normal activities of the hepatic cells, and it indicates a state of functional incompetence second only to that seen with the milder grades of acute yellow atrophy. The origin of the jaundice that usually accompanies this phenomenon is intimately associated with the diminution of the excretion of bile; it is found in the hepatic cell. According to the work of Eppinger and others, the mechanism of the jaundice is an interference within the confines of the cell with the passage of bile components into the bile capillaries. Toxemia of various grades is present.

3. An external biliary fistula from which large quantities of bile escape from the organism for shorter periods of time or smaller quantities escape over long periods of time. Continued or extreme bile wastage leads to other subjective and objective symptoms which are presently to be noted.

4. Obstruction of the common duct. This operates through the profound jaundice which it causes.

5. Deepening or very deep grades of jaundice in the presence of an open common duct or in the presence of a discharging external biliary fistula, especially when the quantity of bile discharged remains constant.

Severe grades of jaundice or deepening jaundice is an important indication of severe lesions and follows and coexists with, or is shortly followed by, changes in the liver cells which lead to undermining physiologic disturbances. Quantitative estimations of the bilirubin content of the blood serum (van den Bergh) are roughly proportionate to the depth of the existing jaundice and are extremely valuable for this purpose in clinical practice. These estimations were constantly employed in these studies.

Many of the items listed in this classification as phenomena associated with a severe type of biliary tract lesion result directly from the presence of jaundice. This includes both subjective and objective phenomena. The most important of these are:

1. Hemorrhage.

2. The presence of renal complications as shown by the laboratory evidences of nephritis (or nephrosis) and by a diminution of the fluid output.

3. The development of acidosis or of an alkalosis.

Combined subjective and objective phenomena occur. These include:

1. Loss of vasomotor function—flagging in the strength of the cardiac function and in the quality and fulness of the pulse.

2. Loss of weight and strength. This is an important item and is due to other factors, such as insufficiency in food and fluid intake, to the loss of bile and to vomiting.

3. Deterioration in the general condition of the patient; lassitude and inaptitude for any exertion—sluggishness of movement, and other symptoms. These, too, parallel other factors and are dependent on them, especially on bile wastage, and form valuable criteria for making judgments.

4. The development of a peculiar form of toxemia ("cholemia") in which sluggishness of the vital faculties and various grades of coma form the most important parts. This always indicates the most severe grade of disease, and unually indicates an approaching fatality. Commonly the toxemia is associated with deep grades of jaundice.

As the severe types of cases under discussion come under observation they are found to fall into two broad groups: the group in which operation was not performed and the group in which operation on the biliary tract had previously been performed.

OPERATION NOT PERFORMED

The group in which operation was not performed contains cases in which the total duration of the symptoms is only a matter of weeks or months; in these it is noted, however, that the progression of the biologic development has been rapid. The symptomatology includes the usual biliary colic and attacks of cholecystitis, fever, possibly chills, initial or later vomiting, loss of weight and strength and at least some of the phenomena included in the preceding classification. Jaundice is almost always present; it usually deepens under observation, is always of severe grade, is frequently accompanied by secondary symptoms, especially hemorrhage, can be followed clinically by the variations of the van den Bergh test and quickly assumes a dominant position in the clinical picture. Renal complications—nephritis, nephrosis (renal epithelium degeneration)—may not be demonstrable. When present, the latter frequently begin as laboratory phenomena, and as such, possibly play no part in the clinical picture; later they can, and do, assume proportions of their own. When there is persistent vomiting there is a consequent diminution in the food and fluid intake which is quickly reflected in a similar or exaggerated diminution of the fluid output; the latter, however, may also be the only indication of renal damage.

All grades of severity are seen in clinical practice. In the most severe cases, there are laboratory evidenecs of an increasing acidosis; finally, a toxemia develops associated with coma, with the deepest forms of jaundice, carphologia, loss of control of the sphincters, Cheyne-Stokes breathing and other symptoms. The cases in which the latter phenomena occur are invariably fatal.

In other cases in which operation has not been performed and in which the disease has existed for a number of years, the individual manifestations—i. e., the attacks of cholecystitis—are separated by variable and fairly long intervals of apparently good health. Finally an attack

occurs in which the manifestations are more marked than the previous ones and in which they assume the characteristics of those described in the preceding paragraphs.

The group in which operation has not been performed also contains cases in which the progression of the illness and its symptomatology is a fairly continuous one. At a certain stage of the development, the symptom complex assumes a severity out of all proportion to the previously existing manifestations, and it becomes similar to that described in the preceding paragraphs.

In the cases in which operation is not performed the transition from a mild or moderately severe form of biliary tract disease to the severe form considered in this discussion is commonly associated with a well defined factor which is easily recognizable in the clinical picture. This change is commonly associated with a more or less complete obstruction of the common bile duct. Case 99 forms a good illustration of this type, and includes illustrative features common to all cases in the group in which operation is not performed.

CASE 99.—A woman, aged 60, had been having attacks of right hypochondriac pain with fever, vomiting and jaundice at irregular intervals for the preceeding five or six years. The present attack resembled the previous ones, except that the general symptoms seemed more severe, the jaundice kept increasing in intensity, the general condition of the patient was becoming increasingly poor and stupor was developing.

The physical examination confirmed these facts: Obstruction of the common duct was absolute; the jaundice was most intense and grew deeper under observation; the patient was stuporous and on the verge of deep coma, and the condition of the circulation and of the general well-being showed marked decomposition and deterioration. Except for some distention, the abdomen yielded no positively abnormal facts. The rest of the physical examination disclosed nothing abnormal. There were laboratory evidences of an acidosis (diacetic acid in the urine) without glycosuria or hyperglycemia. The urine showed the presence of an acute nephritis (albumin, casts and other elements); the phenolphthalein excretion was 10 per cent in the first two hours; nevertheless, the kidney output (1,100 cc.) was sufficient. There was no nitrogen retention (urea nitrogen, 17; nonprotein nitrogen, 28; uric acid, 1; creatinine, 1; cholesterol, 0.32 and carbon dioxide, 48 per cent) in the blood.

The patient received a transfusion with 500 cc. of blood, and large quantities of glucose were given intravenously in a 5 per cent solution. Under these therapeutic measures, there was a remarkable temporary improvement which lasted about twenty-four hours. Then the stupor and coma reappeared and deepened, and the same therapeutic measures were repeated. The improvement thereafter was not nearly so marked. On the morning of the second day, the general condition of the patient was bad; the condition of the cardio-respiratory system was poor; there was deep coma, Cheyne-Stokes respiration and other signs of a profound toxemia. The patient died soon afterward with the typical picture of a "cholemia."

Postmortem examination of the body showed an extensive cholelithiasis occupying the common and major portions of the hepatic ducts, an acute cholangitis, multiple abscesses in the parenchyma of the liver and an acute renal swelling and degeneration of the renal epithelium.

This case illustrates (1) the occurrence of a severe biliary tract lesion in a patient not operated on; (2) the general symptomatology; (3) the presence of subjective and objective symptoms and the laboratory data on which the gravity of the disease is measured; (4) the presence of the determining factor, obstructive jaundice, with which infection is associated in this particular instance; (5) the temporary relief of symptoms after free mobilization of glucose; (6) the occurrence of a secondary renal degeneration, and (7) the terminal toxemia (cholemia), which because of facts to be presently discussed in this communication, especially the absence of blood nitrogen retention, must be assigned for the major part to an hepatic origin and to a much less extent to the renal factor.

In rare instances the transition to the severe type of case is associated with a severe form of infection which almost always assumes the clinical manifestations of an acute yellow atrophy of the liver. Case 100 illustrates this type of case.

CASE 100.—A married woman, who had borne two healthy children and who had previously been free from any attack similar to the present one, was seized two weeks before admission to the hospital with sharp epigastric pain which radiated to the right side of the back and to the scapula; vomiting occurred and fever developed. Three days after the onset, she became jaundiced; the pain and jaundice continued, the urine darkened progressively, and the stools became clay colored. At the beginning of the condition the physician was able to feel a much swollen liver which extended several fingerbreadths below the costal margin; but in the days following, the size of the liver lessened appreciably every day.

On the day of admission to the hospital physical examination showed: (1) a patient who was well nourished and appeared acutely ill; (2) a general tendency to inactivity; (3) sluggish reactions of the various faculties to stimuli; (4) an intense jaundice of the skin and of all of the mucous membranes; and (5) a liver which was palpable below the costal margin, and which had a sharp edge and a smooth and not tender surface. The rest of the physical examination gave no positive abnormal conditions.

Late in the day of admission, the patient suddenly became stuporous. During these few hours, the jaundice increased in intensity; a stool which was evacuated was clay colored, and the liver receded under the costal arch so that it was no longer palpable. There were distinct signs of liver insufficiency; the patient vomited profusely; she was restless and irrational and there were marked twitchings of the face and extremities.

On the next day, the patient was much worse. She was in deep coma. The jaundice was apparently still increasing and she had lost all sphincter control. The vomitus consisted of chocolate-like material. The edge of the liver was not palpable, and its outline was obscured by tympany. Irritative phenomena

occurred, referable to the central nervous system. A uremic odor to the breath was perceptible. Finally there was Cheyne-Stokes breathing. The patiently died shortly afterward.

During the short stay in the hospital there semed to be some restriction in the output of urine; examination of the later showed a heavy trace of albumin. much bile and an occasional white cell in the microscopic field. The Wassermann reaction was negative. The nitrogen status in the blood was as follows: urea nitrogen, 15.4; nonprotein nitrogen, 35; uric acid, 1.3, and creatinine, 1. The blood contained 0.086 gm. of cholesterol per hundred cubic centimeters, and the carbon dioxide content was 40.

The postmortem examination of the body showed: (1) a gallbladder with much thickened walls containing about twenty-five stones lying in a thick, light green, turbid bile, which had a purulent odor; (2) empty cystic and common ducts; (3) thickened and edematous walls of the common duct and a lumen containing bile similar to that in the gallbladder; (4) a normal hepatic artery; (5) negative portal and hepatic veins; (6) a typical acute yellow atrophy of the parenchyma of the liver; (7) several enlarged hyperplastic lymph nodes along the duct; (8) a swollen, congested spleen with enlarged lymph nodes at the hilum; (9) moderately enlarged retroperitoneal and mesenteric lymph nodes; (10) normal suprarenal glands and (11) enlarged, deeply congested kidneys from which the capsules stripped with ease.

We interpret this condition as a case of cholelithiasis in which an acute yellow atrophy of the liver was the terminal phenomenon of an extremely severe infection of the biliary tract. The case is differentiated from the preceding one by the character of the determining factor (infection as opposed to obstruction) and by the lack of recuperative power in the presence of this terminal lesion. It resembles the first case in the remainder of the manifestations. The presence of a low uric acid content in the blood is remarkable. This clinical fact is not in conformity with the observations of Mann and his co-workers who, in experimental work, found high uric acid contents in the blood after removal of the liver.

OPERATION PERFORMED

In the group of cases in which operation has been performed the symptomatology of the severe type of case under discussion parallels closely that given for the cases in which operation was not performed, and the differences, if any, incline themselves to an increase in severity of the individual manifestations or of the total symptom complex regarded as a whole. Many or all of the phenomena classified previously as indicating the severe type of biliary tract disease are constantly present; the patients are extremely sick, and severe forms of toxemia are frequently present.

The group of cases in which operation was performed contains instances in which the transition to the severe type occurs in such close proximity to an operation as to compel the belief that there is a causal relation between some factor associated with the operation and the

appearance of the severe symptoms. One cannot escape the impression that in many cases the anesthetic employed is the most likely factor. The simplicity or severity of the operation which has been performed seems of little importance. Case 96 seems to fall in this group.

CASE 96.—A simple cholecystectomy was performed on a woman for an inflamed gallbladder. The interior of the gallbladder contained a calcareous deposit, and there was numerous pericholecystitic adhesions. A perforation was present in the wall of the gallbladder, and it reached into the parenchyma of the liver. Jaundice was not present before operation, and the kidneys were clinically "normal."

TABLE 1.—*Laboratory Data for Case 96*

			Urine				Blood						
Date	Intake, Cc.	Output, Cc.	Albumin	Casts	Bile	Total Nitrogen, Gm.	Van den Bergh Estimations	Urea Nitrogen	Non-protein Nitrogen	Uric Acid	Creatinine	Cholesterol	Carbon Dioxide, Percentage
June 14	.....	.....	..	..	..	..	.....	....	....	...	...	...	....
15	.....	630	..	..	..	..	.....	....	....	...	...	...	....
16	.....	630	..	..	..	..	.....	....	....	...	...	...	....
17	.....	960	..	..	..	..	.....	....	....	...	...	...	....
18	2,010	1,110	..	..	..	..	.....	....	....	...	...	...	....
19	3,320	1,440	..	..	..	..	.....	....	....	...	...	...	....
20	2,590	1,340	..	..	..	..	.....	....	....	...	...	...	....
21	1,890	1,440	..	..	..	..	.....	....	....	...	...	...	....
22	1,530	1,170	..	..	..	..	.....	....	....	...	...	...	....
23	1,800	1,110	..	..	..	..	.....	....	....	...	...	...	....
24	1,630	1,350	..	..	..	..	.....	....	....	...	...	...	....
25	2,010	1,260	..	..	..	..	.....	....	....	...	...	...	....
26	2,010	1,230	..	..	..	..	.....	....	....	...	...	...	....
27	2,100	1,770	..	..	..	..	.....	....	....	...	...	...	....
28	1,990	1,880	..	..	+	..	.....	....	....	...	...	...	....
29	2,220	1,560	..	..	..	..	.....	....	....	...	...	...	....
30	1,770	1,500	..	..	+	..	.....	....	....	...	...	...	....
July 1	2,100	1,060	Tr.	0	+	..	1:7700	....	....	...	...	...	....
2	2,400	1,500	Tr.	0	..	..	.....	....	....	...	...	...	....
3	2,490	690+	..	..	..	..	.....	....	....	...	...	...	....
4	2,880	1,050+	+	0	..	..	.....	....	....	...	...	...	....
5	2,550	1,380+	++	..	..	..	.....	....	....	...	...	...	....
6	1,580	900+	+	0	..	..	.....	....	....	...	...	...	....
7	1,080	780+	..	..	++	6	1:25000	12.6	31.5	2.0	1.0	0.088	46.2
8	1,680	1,350+	Tr.	..	+	..	.....	....	....	...	...	...	....
9	2,880	1,200	..	..	..	..	.....	....	....	...	...	...	....
10	2,640	890+	Tr.	..	..	..	.....	....	....	...	...	...	....
11	2,250	990+	0	+	..	..	.....	....	....	...	...	...	....
12	840	1,290	..	..	..	..	.....	....	....	...	...	...	....
13	2,820	1,500+	0	+	..	..	.....	....	....	...	...	...	....
14	1,680	720	0	0	..	..	1:110000	12.6	35.0	2.0	1.0	0.094	59.5
15	1,200	?	0	0	..	..	.....	....	....	...	...	...	....
16	1,230	1,080+	..	..	..	..	.....	....	....	...	...	...	....
17	1,740	?	..	..	..	..	.....	....	....	...	...	...	....
28	.....	.....	..	..	..	..	.....	14.0	34.1	2.5	1.0	...	....

Four days after operation, the patient became jaundiced; the condition increased in intensity during the succeeding days, and the stools became acholic. The patient vomited whatever she ingested, and the symptom grew worse concomitantly with the increase in the jaundice. At the end of about ten days, the patient was distinctly stuporous, and the various faculties were distinctly apathetic. Coincident with the appearance and progression of these symptoms, the discharge of bile, which previously had been moderate, became markedly restricted in quantity and consisted of a thick, yellowish, mucoid, extremely turbid fluid.

The main reliance in treatment was placed on (1) transfusions of blood; (2) infusions of 5 per cent dextrose solutions, intravenously, and (3) the administra-

tion of abundant supplies of fluids of all kinds. The symptoms gradually improved, the jaundice lessened, and the vomiting finally stopped; the progressive improvement became permanent, and the patient recovered. At the time of discharge, jaundice was still present but steadily lessening. The laboratory data are given in table 1.

The group of cases in which operation was performed contains instances in which, following operation for the relief of obstruction of the biliary tract (common duct), the previously existing symptoms either do not become ameliorated or become aggravated. The presence of the biliary obstruction makes this a severe case from the beginning, and the lack of improvement after operation and adequate drainage of the common duct is probably related to an advanced pathologic process or an advanced pathologic physiology, or to both of these factors together. The aggravation of the manifestations is undoubtedly often increased by the effects of the anesthetic drug on the renal, and to a lesser degree on the hepatic, parenchyma. A low grade of toxemia is commonly present, with nausea, vomiting, diminution of fluid intake and output and with loss of weight. Fulminant forms of toxemia also occur and a fatal issue follows rapidly. Cases 91 and 104 illustrate this type of case:

CASE 91.—A man, aged 73, had a persistent jaundice preceded and accompanied by pain in the right upper quadrant of the abdomen, with periods of remission in the intensity of the jaundice. Physical examination revealed a slightly enlarged liver and a moderate degree of emaciation, and confirmed the presence of the severe jaundice. A test of the function of the liver showed 30 per cent retention at the end of one hour. The phthalein test averaged between 80 and 90 per cent excretion at the end of two hours. A single obstructing stone found in the common duct at operation was removed; a cholecystectomy was done. In spite of the fact that the wound in the duct was sutured, drainage of bile occurred immediately and was profuse. Convalescence proceded in the customary manner for the first two weeks. There was some diminution in the jaundice at first; but later it increased, and continued to be severe throughout the duration of the illness. On the seventeenth day after operation, the patient began to hiccough and vomit. The appetite grew poorer. The general condition continued to deteriorate in spite of all measures employed, and the patient died at the end of a month. Postmortem examination was not performed. The laboratory data are given in table 2.

CASE 104.—A woman, aged 60, had had numerous attacks of right hypochondriac pain. Several days before admission she had a severe attack of acute cholecystitis, and she became jaundiced. At operation, an acutely inflammed gallbladder was found, and stones were present in the gallbladder and in the common duct. Following operation, the temperature rose rapidly, and the patient developed marked toxemia which seemed clinically to be typically "cholemic." Death occurred one day later. There was no time or opportunity to make laboratory studies, and postmortem examination was not performed.

The group of cases in which operation was performed contains instances in which a simple operation had been performed at an appreci-

able interval before the present moment of observation; the patients had gone through these primary operations—usually a cholecystectomy or cholecystostomy—with no extraordinary manifestations, and recovery had been uneventful. Later, there was a recurrence of symptoms; these reproduced the previously existing symptom complex or presented new manifestations; in any case, the further development of the clinical picture followed along the lines already described in this communication,

TABLE 2.—*Laboratory Data for Case 91*

Date	Intake, Cc.	Output, Cc.	Liver Function Test, Percentage	Nephritis	Urine Bile	Phenolsulphonphthalein Test, Percentage	Total Nitrogen, Gm.	Stool	Stool Urobilin, Gm.	Van den Bergh Estimations	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	Cholesterol	Carbon Dioxide, Percentage
March 9	.....	.....	30	0	+	90	...	..	....	1:50000	18.2	31.5	3.5	1.2	0.266	48
12	480	890	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
13	960	660	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
14	1,920	1,050	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
15	2,490	1,200	..	+	..	80	...	..	....	1:30000	28.0	....	2.5	1.3	0.170	..
16	2,220	1,080	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
17	1,980	1,020	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
18	1,800	1,080	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
19	2,160	1,200	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
20	2,220	1,200	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
21	1,950	1,520	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
22	1,680	1,440	..	....	..	76	...	Brown	....	1:50000	....	....	...	...	.....	..
23	1,200	1,080	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
24	1,500	1,200	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
25	1,980	1,740	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
26	2,240	1,500	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
27	2,640	1,870	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
28	2,640	1,040	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
29	3,120	660	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
30	3,750	1,140	..	....	..	45	6.6	..	....	.....	....	....	...	...	.....	..
31	3,840	1,050	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
April 1	720+	300	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
2	2,130	300	..	....	..	..	...	..	....	.....	22.4	....	2.5	1.2	.....	..
3	2,730	360	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
4	3,420	480	..	....	..	..	...	..	0.045	.....	....	....	...	...	.....	..
5	3,150	720	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
6	2,640	750	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
7	2,820	1,440	..	++	..	..	...	..	....	.....	22.4	52.5	2.5	1.3	0.206	60
8	2,670	960	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
9	2,700	480	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
10	1,020	840	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..
11	600	480	..	....	..	..	...	..	....	.....	....	....	...	...	.....	..

both in the unoperated and in the operated groups of cases. Some form of obstruction of the common duct is usually present in these cases. Commonly the obstruction is due to stones; less frequently to tumor, especially a carcinoma of the pancreas or of the common duct at the papilla; more rarely to stricture of the common or hepatic ducts. Frequently, the patient's condition continues at a relatively low status for a certain length of time until some particular factor causes a sudden change for the worse and finally death.

TABLE 3.—*Pathologic and Laboratory Data of All Cases in This Communication*

Case No.	Liver Lesion	Phenol-sulphon-phthal-ein Test	Ne-phritis	Jaun-dice	Urine Bile	Van den Bergh Icteric Index	Urea Nitro-gen	Non-pro-tein Nitro-gen	Uric Acid	Creat-inine	Phenol-sulphon-phthal-ein Test	Ne-phritis	Jaun-dice	Urine Bile	Van den Bergh Icteric Index	Urea Nitro-gen	Non-pro-tein Nitro-gen	Uric Acid	Creat-inine	Result
4	Infiltration	....	0	0	0	.....	12.6	30.9	1.3	1.1	....	0	0	0	.....	15.4	35.0	2.0	1.0	Well
75	Chronic cholangitis; fat infiltration; cholemia	....	+	..	+	.....	21.0	60.0	2.2	1.1	....	+	..	+	.....	21.0	40.0	2.3	1.5	Died
55	Infiltration	....	0	0	..	.....	18.2	36.7	2.6	1.1	....	+	+	0	1: 40000	63.0	122.5	6.5	1.3	Well
60	Cirrhosis	....	0	0	0	1:200000	15.4	34.1	2.5	1.0	....	0	0	0	.....	18.2	35.5	2.5	1.0	Well
86	Chronic pericholangitis	....	..	..	0	1:120000	22.4	51.2	3.9	2.0	....	..	..	..	1:400000	19.6	45.5	3.5	1.2	Well
90	Fatty infiltration; passive congestion	....	0	..	+	1: 5000	14.0	35.0	2.8	1.3	....	+	..	+	.....	40.6	94.4	3.0	1.0	Died
91	Cholangitis; degeneration	....	0	+	+	1: 50000	18.2	31.5	3.5	1.2	....	+	+	+	1: 30000	22.4	52.5	2.5	1.3	Died
85	Necrosis; purulent cholangitis	....	..	0	+	1: 78000	18.2	35.0	4.0	1.1	....	..	..	..	.....	....	....	Immediate		Died
71	Early cirrhosis	....	+	..	0	.....	22.4	66.3	2.7	1.8	....	..	..	..	.....	....	....	...	...	Well
81	Acute suppurative cholecystitis	80%	0	0	..	.....	29.4	57.7	3.3	1.0	....	+	..	..	.....	29.4	61.0	3.0	1.0	Well
82	Empyema; stones; obese and sick	....	0	0	?	1:150000	23.6	50.0	2.5	1.0	....	..	..	..	.....	....	....	...	...	Died
98	Cholecystitis; postoperative vomiting	....	..	..	..	.....	....	....	...	...	....	+	..	..	.....	54.6	129.5	2.4	1.2	Well
97	Acute cholecystitis; exacerbation; slight postoperative acidosis	70%	0	+	+	1:200000	....	....	...	...	....	++	..	++	.....	65.8	136.7	7.5	2.4	Well
99	Duct obstruction by stones; jaundice cholangitis with multiple abscesses of the liver; abscesses in the lung; acute renal swelling and nephritis; acidosis; carbon dioxide, 48%	10%	++	+++	+	1: 5000	17.0	28.0	1.0	1.0	No operation									Died
100	Chronic cholecystitis; acute yellow atrophy; renal congestion; cholemia	....	0	+	+	.....	15.4	35.0	1.3	1.0	No operation									Died
96	Chronic cholecystitis; pericholecystitis; pericholecystitis with perforation into liver; postoperative jaundice with cholemia	....	0	0	0	.....	....	....	...	...	....	+	+++	++	1: 7700	12.6	31.5	2.0	1.0	Well
94	Chronic cholecystitis; postoperative vomiting, nausea, etc.; toxemia	....	..	..	..	.....	....	....	...	...	15%	+	+	+	1: 50000	109.2	140.0	11.0	2.0	Well
80	Degeneration	....	+	0	..	.....	29.4	....	5.3	2.0	....	..	..	..	.....	....	....	...	...	Died

LABORATORY OBSERVATIONS

Table 3 contains all of the available pathologic and laboratory data of the cases studied for this communication. The cases were selected only for the severity of their clinical and other manifestations, but were otherwise taken seriatim as the patients were consecutively admitted and discharged from the hospital. In all of the studies, special attention was paid to the surgical problems involved as they were related to the study of the blood chemistry.

A summary of the deductions to be made from this table include the following:

1. The severe type of biliary tract disease is almost invariably associated with definite changes in the parenchyma of the liver.

2. The severe type of biliary tract disease is more commonly associated with jaundice and with renal changes than the mild or moderately severe type of case.

3. The preoperative nitrogen body content of the blood does not differ markedly from that in mild and moderately severe cases of biliary tract disease. This seems to hold good, at least as far as the cases studied in this communication are concerned, both for the blood figures as a whole and for the individual groups.

4. The postoperative nitrogen body content of the blood shows, consistently, increases over the preoperative status; these follow along the line outlined in the preceding papers. A decrease occurs after operation in only one instance in the cases in the table. In at least one-third of the cases these increases are extremely large.

5. When large postoperative increases of the nitrogen body contents of the blood occur after operation, the blood figures have been reliable indications of the gravity of the entire clinical picture; subsequent regression to normal levels has accompanied amelioration of the pathologic condition, either temporary or permanent; their progression has indicated an equal progression of the illness.

6. The prognosis in the severe type of biliary tract disease is extremely grave; 41 per cent of the cases studied in this communication have terminated fatally.

The following cases illustrate the relationship of the various clinical and laboratory data on which a discussion of the problem is based.

Case 75 illustrates the relation of the fluid intake and output in this group of cases to the blood figures.

CASE 75.—A cholecystectomy was done after an acute exacerbation of a chronic cholecystitis; cholelithiasis was present also. Laboratory evidence of a moderate nephritis was present. During the acute attack, the patient became

jaundiced, and bile in moderate amounts was present in the urine. The laboratory data are given in table 4.

There was no apparent increase in the nephritis after the operation. No change was noted in the degree of jaundice. About ten days later, the patient's appetite began to flag; this condition increased and became associated with vomiting. A free discharge of bile occurred from the wound, and bile continued to pass into the intestinal tract. Acidosis developed later, which was probably due to the marked restriction in food and fluid intake. There was a tendency to diminution in the fluid output of the body. The symptoms continued, and the patient finally

TABLE 4.—*Laboratory Data for Case 75*

Day of Illness	Clinical Notes	Nephritis	Acetone	Diacetic	Jaundice	Urine Bile	Van den Bergh Estimations	Fluid Intake, Cc.	Fluid Output, Cc.	Urea Nitrogen	Non-protein Nitrogen	Uric Acid	Creatinine
Ante-operative		++	..	..	+	+	.....	.....	.....	21.0	60.0	2.2	1.1
September 4, operation													
Postoperative													
Sept.													
6	.....	++	..	..	..	+	.....	3,300	?	21.0	40.0	2.3	1.5
7	.....	..	..	..	..	..	.....	6,400	1,140+	....	....	...	...
8	Pneumonia	..	..	..	..	..	.....	3,000	1,200+	...?	....	...	...
9	.....	..	..	..	..	..	.....	1,080	?	....	....	...	...
10	.....	+	..	..	..	..	.....	1,200+	1,140+	14.0	34.1	1.6	1.0
11	.....	..	..	..	..	..	.....	1,380	1,170	....	....	...	...
12	.....	..	..	..	..	..	.....	2,340	1,500	....	....	...	...
13	.....	..	..	..	..	..	.....	2,100	1,740	....	....	...	...
14	.....	..	..	..	..	..	.....	2,040	1,020	....	....	...	...
15	No bile drainage	+	..	..	..	..	.....	2,160	1,740	14.0	....	1.6	1.0
16	.....	..	..	..	..	..	.....	2,100	2,220	....	....	...	...
17	.....	..	..	..	..	..	.....	2,040	1,800	....	....	...	...
18	.....	..	..	..	..	..	.....	1,440	1,380	....	....	...	...
19	Profuse bile drainage	..	..	..	..	..	.....	1,780	1,440	....	....	...	...
20	.....	..	..	..	..	..	.....	1,380	1,380	....	....	...	...
21	.....	..	..	..	..	..	.....	1,440	1,380	....	....	...	...
22	Complete anorexia; nausea; vomiting; free discharge of bile; bile in stool	..	..	..	..	+	1:70000	1,200	?	18.2	34.2	2.7	1.2
23	.....	..	..	..	..	..	.....	720	600	....	....	...	...
24	Symptoms continue as on September 22	+	+	+	..	+	.....	540	600	....	....	...	...
25	.....	..	..	..	..	..	.....	720	900	....	....	...	...
26	.....	..	..	..	..	..	.....	360	1,140	....	....	...	...
27	.....	..	..	..	..	..	.....	840	1,380	....	....	...	...
28	.....	..	..	..	..	..	.....	600	1,140	....	....	...	...
	Ceased												

died. The increase in fluid output during the last few days of life must be accepted as evidence that the excretory mechanism of the body was begining to recuperate.

The postmortem examination of the body showed a marked fatty infiltration of the liver with marked fibrosis around the portal spaces; there was no acute inflammation. There were changes in the kidneys also.

CASE 94.—The patient was first operated on in 1914 at the age of 36. At that time a large stone was found in the common duct, and much bile sand was present throughout the demonstrable portions of the biliary tract. A cholecystectomy was done and the ducts were drained; the patient recovered. In 1922, he began to have attacks of typical biliary colic with jaundice and clay colored

stools, nausea, chilliness and fever. In 1923, he was operated on again. Stones had again formed in the common duct, and the walls of the duct were enormously thick. The stones were removed, and drainage of bile from the common duct was instituted.

At the end of the first week after operation he began to vomit, and his general condition began to deteriorate. Ten days after operation, the drainage of bile had become scant. Signs of a nephritis developed. Five days later, signs of toxemia (uremia?) were marked. Under conservative forms of treatment (5 per cent dextrose infusions, blood transfusion, forcing of fluids generally) these symptoms gradually disappeared, and the patient finally recovered.

The postoperative laboratory data are given in the chart.

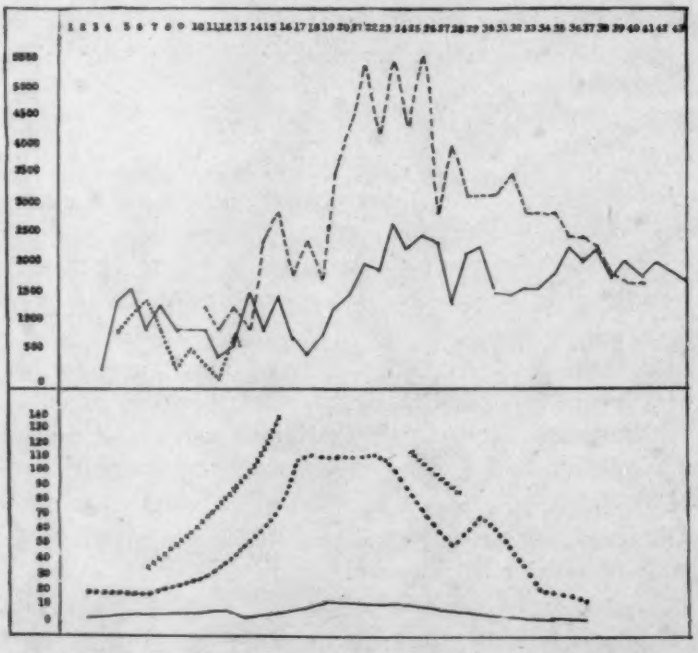


Fig. 1.—Laboratory data in case 94. In the upper part of the chart, the broken line indicates the food and fluid intake; the unbroken line, the fluid output, and the dotted line, the bile drainage. In the lower part of the chart, the dotted line indicates milligrams of urea nitrogen per hundred cubic centimeters; the crosses, the nonprotein nitrogen, and the unbroken line, the uric acid.

CORRELATION OF CLINICAL AND LABORATORY FACTS

The segregation of the group of cases embodied in this communication has not been simple. Various difficulties have arisen, not the least of which has been the selection of the cases in which the progression of the disease has been sufficient to enable one to classify it as a severe case. Cases have occurred constantly which at first sight have appeared to be mild cases or moderately advanced cases, and in which the later development of the clinical picture or the nature of the postoperative

phenomena have compelled the inclusion into the severe group. The opposite has happened also. As far as possible, only those cases are included in which we have been sure of our ground.

The chief reason for this difficulty lies in the enormous compensatory activity of the liver and its associated organs, especially the kidneys. Laboratory evidence is abundant in proving this point. Far advanced pathologic processes therefore may and do occur before an adequate symptomatology is presented to the clinician; this is true not only as far as subjective and objective symptoms and manifestations are concerned, but even more so of laboratory evidence. In all of the studies in this and in the previous communications, this factor has been extremely important and has interfered markedly with the proper valuation of the demonstrable evidence.

The outstanding facts in these studies are:

1. The comparatively restricted field in which the results of biliary tract lesions have established effects when the duration of the disease has been short and the manifestations of the disease could be classified as "mild." In the early stages of lesions of the biliary tract, there have been few pathologic changes and, for practical purposes, no physiologic changes have occurred.

2. In the mild cases, the total absence of complicating factors, especially of jaundice and renal changes. These begin to establish themselves in the group of moderately advanced cases, and assume their greatest frequency as the cases present more and more of the severe manifestations.

3. The great frequency with which the severe manifestations are associated with obstructive jaundice.

4. The relative frequency with which the case has passed from a mild or moderately severe form to the severe form discussed in this communication directly after operative intervention.

5. Most, if not all, of the primary physiologic disturbances are due to secondary effects on the hepatic cell.

The first disturbances that have been perceptible have seemed to us to be best demonstrable by the van den Bergh test. The changes have been present not only when the jaundice has been of the mildest degree, but even when no discoloration could be seen either in the skin or in the conjunctiva. These subicteric conditions are commonly present in the absence of gross obstruction in the hepatic or common ducts and seem to indicate changes in the hepatic cell itself. Physiologically, hepatic cell change seems to be synonymous with obstruction of the capillary ducts; the hepatic cell is the only structure present which could cause obstruction of these ducts; this seems to be true from clinical observa-

tions and has been demonstrated experimentally. In this respect, the status of the van den Bergh test has acted as an indicator of the state of function of the hepatic cell.

In the cases included in this study, biliary tract disease was constituted primarily by calculus-producing conditions either in the absence of, or associated with, infection. The lithiasis which results from disturbance of the cholesterol metabolism practically always originates in the gallbladder and is primarily free from the influences of bacterial infection; the absence of the latter symptoms are due to the attempted or consummated passage of stones, as foreign bodies, from the gallbladder; in such cases we have no clinical evidence that reflex disturbances have occurred in the hepatic cell. The latter disturbances occur only under three conditions. (1) when infection is added; (2) when obstruction occurs and (3) when both of these complications exist together. The variations of the van den Bergh test that we have obtained, when either or both of these two factors have been added, have indicated that in their presence disturbances of hepatic function frequently occur.

The presence of stones in the biliary ducts—especially the hepatic and common bile ducts—interferes with the free passage of bile into the intestine. The difference between the effects of the latter and of a complete obstruction is only one of mathematical proportion. An important item to remember is that infection is frequently present with a nonobstructive or obstructive stone in the duct system. An important deduction of this study has been that the presence of stones in the duct system must be productive of some interference in physiologic function (case 94). This possibly accounts for some of the wide variations in the nitrogen bodies in the blood present before any operative intervention and explains the apparent inability to classify these figures properly. In any case these may seem to be of little or no clinical importance for the moment, owing to the compensatory activity of the liver and associated organs. This functional inhibition is comparable to that demonstrable in the urinary apparatus under similar calculus conditions, as shown by the excretion of indigo carmine; in the latter, however, the happy incidence of a bilateral organ in the presence of a unilateral disease facilitates a more accurate determination of functional change by comparisons of the affected and the sound sides.

The changes in the van den Berg test and the status of nitrogen bodies in the blood in cases in which infection and obstruction were factors are shown in tables 5, 6 and 7.

6. Evidence of renal damage has been present frequently; it was present in eighteen of twenty-eight cases. The clinical and laboratory facts have suggested the following classification:

(*a*) In most of these instances the renal damage as a preexisting condition was mostly a laboratory phenomena and did not have any apparent relation to the primary biliary tract or secondary hepatic cell lesion.

(*b*) In 33 per cent of the cases the renal damage was associated with jaundice. Undoubtedly in a few of these the renal lesion was independent of the pathologic condition of the biliary tract or hepatic cell as described

TABLE 5.—*Effect of Mild Forms of Infections on Hepatic Functions**

Case No.	Age	Van den Bergh Estimations	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	Blood Cholesterol
34	32	1:120000	15.4	35.8	2.0	1.0	0.142
56	48	1:100000	14.0	....	2.7	1.3	0.160
58	30	1:150000	18.2	35.2	2.2	1.0	0.142
59	35	1:2000000	15.4	34.1	2.5	1.0	0.200
60	..	1:2000000	15.4	34.1	2.5	1.0	0.176
61	25	1:1000000	15.4	35.8	2.0	1.0	0.090
82	40	1:1500000	26.6	50.0	2.5	1.0	0.124

* Infection was indicated by the local pathologic changes and other clinical and laboratory evidence. All of the patients were somewhat jaundiced.

TABLE 6.—*Effects of Severe Forms of Infection on Hepatic Function*

Case No.	Infections	Van den Bergh Estimations	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	
91	Cholangitis with degeneration	1:5000	14.0	35.0	2.8	1.3	Died
99	Cholangitis; multiple abscesses	1:5000	17.0	28.0	1.0	1.0	Died; no operation
85	Purulent cholangitis; necrosis	1:78000	18.2	31.5	3.5	1.2	Died

TABLE 7.—*Status of the van den Bergh Test and the Status of Nitrogen Bodies in the Blood in Cases of Obstruction of Common Duct**

Case No.	Age	Van den Bergh Estimations	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	Blood Cholesterol	
27	63	1:10000	14.0	33.3	2.5	1.1	0.170	
101	63	1:14000	15.4	29.3	2.5	1.0	0.136	Died
102	..	1:20000	12.6	33.3	2.0	1.0	0.348	
103	65	1:20000	?	....	...	...	.....	Died

* All of the patients were deeply jaundiced.

in the preceding paragraph. In a few, however, the evidence seemed conclusive that the jaundice had an etiologic relationship to the renal damage. Table 8 illustrates this relationship.

In a few cases the renal damage resulted from the use of the anesthetic (ether). Probably a two-fold mechanism was operative here: there was either a primary effect on the parenchyma of the kidney, or the renal effect was secondary to a primary effect on the liver. In the case on which table 8 is based, the biologic sequence included a primary hepatic effect with deep jaundice followed by secondary renal damage.

Table 9 contains the cases in which jaundice and renal damage coexisted, and shows the status of the van den Bergh test and the status of the content of nitrogen bodies in the blood.

Important deductions to be made from a consideration of the renal aspect of this study include the following:

(*a*) The severity of the renal damage was clinically not always proportionate to the depth of the jaundice. There were cases with mild jaundice in which the renal damage seemed to be excessive.

(*b*) Nitrogen body retention does not always occur in the presence of the renal damage; this seems to follow the observations in cases of

TABLE 8.—*Relationships of Jaundice to Renal Damage*

	Jaundice	Icteric Index	Urine Bile	Albumin	Casts
September 7	+	.....	+	0	0
8	++	1:18000	±	..	..
10	++	1:1600	±	0	0
11	+	.....	..	0	0
14	..	1:1800	..	..	..
19	..	1:17500	..	..	..
20	++	.....	++	vft.	0
21	..	1:44000	..	..	..
22	Operation				
25	+++	.....	++++	++	±
28	..	1:22000	..	..	..
30	..	.....	++	ft.	0
October 2	Fading rapidly	1:66000	..	..	..
7	..	1:140000	..	0	0

TABLE 9.—*Status of van den Bergh Test and of Nitrogen Bodies in the Blood in Cases in Which Jaundice and Renal Damage Coexisted*

Case No.	Age	Jaundice	Urine Bile	Nephritis	Van den Bergh Estimations	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	
101	21	+++	+++	±	1:40000	12.0	33.3	2.5	1.0	Died
102	63	+++	+++	+++	1:7000	14.0	33.3	2.5	1.1	
103	38	+++	++	++	1:18000	11.2	35.8	3.5	1.0	
90	55	+	+	+	1:30000	22.4	52.5	2.5	1.3	Died
55	28	+	?	±	1:40000	63.0	122.5	6.5	1.3	
23	22	+	+	+	1:300000	....	112.0	5.0	2.0	

nephritis which occur in conditions unassociated with biliary tract and hepatic cell lesions.

(*c*) Nitrogen body retention occurs in about 50 per cent of the cases in this group; here it assumes its largest proportions. There is not only a relative increase, but a large absolute increase in the nitrogen bodies in the blood.

SUMMARY AND COMMENT

In summing up the facts outlined in the preceding part of the paper, it appears that the biologic sequence of events of the entity that has its inception in biliary tract disease includes: (1) an initial lesion in the biliary tract, calculi, infection, (2) a primary effect on the hepatic cells leading to physiologic disturbances in the liver, and (3) a secondary

effect in the renal apparatus which leads to an acute degeneration of the renal epithelium—acute nephritis (?), acute nephrosis (?).

Terminal manifestations occur in the second and in the third stages and especially after operative intervention. Death after operation cannot always be explained by surgical trauma or by the development of sepsis. Cases in which death occurs may be divided into two main classes, the chief differentiation being an outspoken kidney insufficiency. Our experiences have paralleled those of Heyd, and we have divided the first class into subgroups.

The first group is made up of patients who have been chronically jaundiced. Following operation convalescence progresses normally up to approximately the fourth or the fifth day, when a slight degree of somnolence appears. Stupor then slowly develops, and in from twelve to twenty-four hours coma intervenes. The temperature rises to 103 or 104 F. The jaundice remains unaltered or sometimes increases in intensity, but kidney function remains adequate, and there is no abnormal retention of nitrogen bodies in the blood. The condition cannot be assigned to dehydration or to bile wastage from an external biliary fistula. We believe that these are cases of liver exhaustion similar to the terminal stage of portal cirrhosis or to acute yellow atrophy of the liver.

The second group consists of those who are not jaundiced, as a rule, and who give a long history of infection of the gallbladder or biliary duct; various types of operation have been performed. The temperature rises to 104 or 105 F., with marked acceleration of the pulse. A peculiar toxemia develops with subsultus tendinum carphologia and talking delirium. Preoperative chemical examination of the blood discloses no abnormality, and the status does not change after operation.

The second class comprises cases in which the clinical pictures presented are similar to those enumerated previously in the first class, except that the evidences of renal damage are now present, that there is a distinct change in the amount and character of the urine excreted, and that there is marked retention of nitrogen-containing elements of the blood.

It is evident that a dysfunction of the liver and of the kidney are responsible for the clinical picture. From the clinical and laboratory observations that we have made, the assumption seems correct that the cases in the first class owe their manifestations to an advance of the biologic entity under discussion to the second stage, i. e., liver dysfunction. Similarly, the conclusion seems correct that the cases in the second class owe their additional clinical and laboratory phenomena to an advance of the disease to the third stage, i. e., renal insufficiency. The peculiar terminal toxemia which occurs presents a distressing symptom complex and is varied in its manifestations; it has been termed cholemia, because of diagnostic ignorance. Literally, cholemia means "bile in the

blood," a condition present, however, in all cases of jaundice even when toxemia is absent. Walters and William Mayo have suggested terms such as "cholemic hepatitis" or "cholemic nephritis" to indicate the existing pathologic condition. While the term "cholemia" might be appropriately used for the conditions described in the second stage, it seems even better to drop the use of this term altogether and to employ the phrase "hepatic toxemia" to describe what actually happens. Similarly, the phrase "renal toxemia of hepatic origin" might better describe the conditions in the third stage.

The physiology of the liver and the kidney are intimately and inseparably related, for the maintenance of the chemical status of the blood components and the life of the person depend on their cooperation. Any impairment of function of the one throws an added burden on the other, and if both are severely diseased, the resultant effects are obvious and manifested by changes in the chemical analysis of the urine and the blood and by the clinical course of the disease.

The liver has many functions, some of which are indirectly dependent on the cooperation of the kidney. As an organ, it is indispensable to life. Animals cannot live without the liver; if this organ is extirpated, as was done by Mann and his co-workers, death ensues within a few hours with symptoms of weakness, muscular twitchings and convulsions, often terminating in coma and occasionally accompanied by anuria. The margin of safety in hepatic disease is tremendous, as the partially ablated livers of experimental animals and the cirrhotic organs of alcoholic persons well bear witness. The margin of safety in pathologic conditions of the kidney while large, cannot be compared to that of the liver. It is highly probable that in hepatic disease some of the catabolistic products of liver metabolism and the end-products dependent on its injury are not without their effect on kidney tissue. For this reason, the clinical picture of uremia is often so closely associated with that of cholemia or hepatic toxemia. This was ascertained experimentally by Grudlinear, who injured the liver by tying off the left portal vein; although there was a compensatory hyperplasia of the remaining healthy tissue, many of the animals succumbed with uremic symptoms, urinary examination revealing albumin and cylindroids and occasionally blood. Similarly, if the hepatic artery is experimentally ligated, necrosis of the liver results, usually accompanied by an anuria. This anuria, which is not reflex, in most cases is the result of direct toxic trauma on the kidney and of a consequent acute nephritis.

From these classic experiments, it is fair to assume that efficient kidney function is partially dependent and maintained by the unrestricted activity of a normal liver. When the liver is organically impaired so that its excretory bodies are shunted through the renal circulation, the kidney invariably suffers, and when hepatic activity

ceases entirely, there is usually renal suppression; in other words, the chemical tests of kidney function in many far advanced cases of liver disease may actually mirror the efficiency of the liver. Most surgeons, in calculating the operative risk, disregard the liver as a factor because its activity cannot be judged clinically by sufficiently reliable simple tests. No one would operate in a case of nephrolithiasis without an evaluation of the stability of the kidney, but cases of cholelithiasis are considered as disease of the gallbladder and as being independent of any consequent liver dyscrazia.

One of the most important deductions from our studies has been that there is a close interrelationship between biliary tract disease (cholelithiasis, infection) and hepatic dysfunction. The corollary which follows closely is that every case carries with it potentialities for kidney damage (renal cell degeneration). The conditions and substances which cause these kidney changes are not definitely known; however, our clinical studies have brought the conviction that periods of jaundice intensify diminished renal function.

The relationship of jaundice to nephritis has always excited interest. In most cases of gallbladder disease jaundice is due to obstruction of the common duct. The bile blocked in the biliary channels is resorbed through the lymphatics and thence enters the blood stream, in which the various products, toxic and otherwise, are excreted by the kidneys. But jaundice may appear without obstruction of the common duct; it is seen in cholangeitis or acute hepatitis accompanying the more severe types of gallstone disease.

In these cases, there is a big difference between dynamic and mechanical icterus. In the former, the bilirubin found in the serum is that which after its manufacture has been taken up by the blood, escaping its excretion by the liver cells. According to the researches of Eppinger, there are certain cases of jaundice in which an apparent mechanical obstruction to the flow of bile is lacking, but jaundice still exists, owing to biliary thrombi in the wider biliary ducts. In other cases these are absent; then the difficulty is said to be a disability on the part of the hepatic cell to allow the bile components to pass through.

Much pathologic evidence has been accumulated to prove that the bile pigments thus retained in the circulating blood not only mechanically plug the uriniferous tubules and interfere with their efficiency, but actually injure the epithelium of these excretory channels. Moelius, studying the autopsy material obtained from jaundiced patients, noted that the bile pigment appeared to collect in the loops of Henle and in the collecting tubules. Charin discovered the pigment in the epithelium of the malphigian corpuscles and Lichtwitz, in the kidney tubules. Examination of the urine in cases of catarrhal jaundice and in cases of marked obstruction of the common duct frequently discloses the presence

of casts. With the exception of the mechanical features of the jaundice, the actual chemical damage caused by certain components of the bile cannot be denied. Cholate, a constituent of the bile when excreted through the kidney, causes damage. Werner has investigated the effects of bile pigments and bile acid salts by injecting them into animals. The latter cause a more severe reaction of the kidney. While Werner was convinced that bile acid salts were the harmful agents in animals, he felt assured that the bile pigments caused injury to the human kidney by obstructing the uriniferous tubules. However this, is open to debate, because many believe that the bile acid salts are the agents harmful to kidney efficiency.

Analysis of the blood in these cases reveals a higher percentage of bile salts than of bile pigments and increase in the cholesterol. The bile salts presumably hold the cholesterin and the lecithin of the bile in solution, so that the increase of both these substances in the blood is probably protective. The increase in the bile salts leads to changes in the other organs, especially in the heart and kidneys, causing profound functional changes. In these cases the urine shows a greater concentration of bile salts than of bile. After a cholecystostomy, however, examination of the urine reveals a daily decrease in the bile salts with an increase in the amount of bile.

An important deduction made in our study is that clinically anesthetic drugs frequently intensify hepatic and renal physiologic disturbances. Colonumal and Ascoli have advanced an interesting and plausible theory. The kidney is damaged and sensitized to a variable degree in excreting the toxins derived directly and indirectly from the destruction of liver tissue. The anesthesia increases the amount of liver tissue toxins until they have reached such an amount that anaphylaxis occurs, resulting in a cessation of kidney function. It is evident then that not only is there a basis for kidney deficiency in many cases of cholelithiasis, but that anesthesia and operation may convert a working balance into a pathologic one.

According to Kehr, parenchymatous degeneration of the kidney caused by bile is further augmented by anesthesia and operation to such an extent that anuria may result. According to von Haberer and Stahler, jaundice as such is only an incident, but previous injury to the liver with its resultant toxemia is the cause of kidney insufficiency, which becomes intensified by operation and anesthesia. The depressing effects of anesthetics on kidney function are well known. Chloroform, of course, is a notorious kidney poison; Colp has shown that ether in prolonged operations is not without its harmful effects, although von Brun claims that there are no observations pointing to death from parenchymatous injury due to poisoning with ether.

Our studies have inclined us to believe that in many cases these hepatic or hepatic-renal physiologic disturbances are fatigue phenomena. It seems highly probable that much abnormality can and does often occur which does not show any perceptible evidence at the bedside or in the laboratory because of the enormous compensatory powers of the liver. However, when the limit of tolerance is reached, the entire mechanism breaks down; only then is definite evidence presented to the clinician. This explains the prompt recuperation after marked physiologic disturbances, such as follows the free drainage of bile in obstructive jaundice or the injection of dextrose when the intravital mobilization of sugar is interfered with; it also explains the prompt disappearance of the signs of renal damage coincidently with improvement of the primary hepatic condition.

It is amazing that the incidence of renal suppression or anuria is not greater. The plausible explanation lies in the remarkable regenerative power of liver tissue, so that the added burden thrown on the kidney is usually not sufficient to cause it completely to suspend its activities. Ante-operative chemical examination of the blood revealing nitrogen retention should be carefully evaluated. This retention may be interpreted as indicative of severe kidney deficiency, but the question should immediately present itself as to whether the breakdown is primarily kidney, or kidney secondary to hepatic, insufficiency. A high blood urea content does not mean, however, that the physiologic condition of the liver is normal or within normal limits, because the smallest possible rests of liver tissue can call forth its manufacture from the simplest ammonia salts, and urea formation is possible just before death. But since the destruction of uric acid depends on the liver, increased amounts of uric acid are fairly characteristic of failing power of the liver, and great importance should be attached to the increase of this protein in the blood. The volume of urinary output is not of great importance, unless there is actual suppression, because it is usually dependent on the amount of fluid intake, and blood figures are altered little by changes in water balance.

Nitrogen retention in the blood is not characteristically restricted to the changes occurring in this particular group of cases of biliary tract disease. The presence of high blood figures, accompanied by changes in the kidney simply represents a series of physiologic reactions to severe forms of intoxications, not infrequently seen in other and widely different conditions, such as severe burns, various drug poisonings and high intestinal obstructions. The impression is conveyed either that some common protein toxic body becomes available in these conditions which fails to become properly detoxified in the liver and affects the kidney, or that various allied or unrelated toxic bodies are formed which, because of a common mechanism or because of elimination of the liver

factor, cause secondary renal changes with which the retention of nitrogen in the blood is associated. In the cases of biliary tract disease that we have studied the jaundice seems to be the preexisting condition which is responsible for the renal damage. Unlike results which can be produced artificially in experimental work, true anuria seldom occurs in clinical practice; but all grades of renal disturbances are recognizable.

The conclusion seems certain that the cases in which retention of nitrogen in the blood is marked form but a small proportion of all cases in which renal damage occurs, and that this abnormality of the blood indicates great disturbances in the interdependent physiologic processes of the liver and the kidney. As indicated previously, the clinical symptoms and the physiologic changes may indicate severe and, possibly, fatal lesions in the primary, *hepatic* stage of this biologic entity; in these cases retention of nitrogen in the blood is not demonstrable. The occurrence of retention and its continued progression should bring sharply to the attention of the clinician the fact that he is dealing with the terminal, *renal* stage of this biologic entity—a lesion that is fatal unless the patient obtains relief from the primary condition before recovery becomes impossible.

The experiences on which the points of view and conclusions in this communication are based are derived from observations on patients admitted to the service of Dr. A. V. Moschcowitz at Mount Sinai Hospital and on patients in private practice.

DERMOID CYST OF THE MEDIASTINUM*

S. L. CALDBICK, M.D.
EVERETT, WASH.

Dermoid cyst of the mediastinum is a rare, but definite, clinical entity. Each case observed should be reported as fully as possible, and because I have had the opportunity to study such a case and have operated successfully on the patient, I believe that a review of the literature, with conclusions as to diagnosis and treatment, will not be out of place.

From a study of the literature, I am led to believe that the only relief for the condition is surgical removal. Of the 119 cases reported, the condition has been found in the majority at autopsy. Beye's [1] statistics show that fifty-seven, or 47 per cent, of the patients were operated on by drainage or removal. The majority of the cysts were drained and removed at subsequent operations. Of these fifty-seven cases, there was recovery in twenty-two instances, improvement in seventeen, death in twelve, and the outcome was not stated in five. This is a mortality of 22 per cent; as operative procedure is the only means by which relief can be obtained, this can not be considered a high mortality. It is not out of proportion to the chance of relief which is offered in an otherwise hopeless condition.

Dermoid cysts of the mediastinum must be differentiated from other tumors of the mediastinum and from aneurysm, tuberculosis and empyema. While pain, cough and embarrassed breathing may suggest the condition, diagnosis can be established definitely only by aspirating the tumor and finding the characteristic glycerin-like fluid, with or without hair. The yellowish fluid which contains grumous material, epithelial cells and fat droplets, is characteristic, and its physical appearance gives more information than its chemical composition.

The embryologic origin of dermoid cysts of the mediastinum is not definitely known. Scammon advances a logical explanation, as follows: In the embryo, the lateral surface of the neck is indented by a series of four (paired) branchial (gills) grooves, which are separated by the branchial (gills) arches. The upper part of the first of these grooves is deepened to form the external auditory meatus. The regions corresponding to the second, third and fourth grooves become deepened, forming the cervical sinuses, which soon close and disappear. Instead of disappearing, a sac of epithelium from the lower grooves may be left unobliterated in the region of the superior mediastinum. The growth from this misplaced epithelium is supposed to form the dermoid cyst.

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* Read before the Pacific Coast Surgical Association, Feb. 25, 1927.

1. Beye, H. L. Ann. Surg. **83**:577 (May) 1926.

SYMPTOMS

There is no sex preponderance in the occurrence of dermoid cysts, and they may be found at any age, but the symptoms usually occur between the ages of 15 and 30. The symptoms are usually caused by pressure from the growing dermoid. Increase in size with development of symptoms may follow a blow on the chest; it may occur after an acute infection, producing an intrathoracic inflammatory process, or it may result from the established individuality of the cyst, as in other parts of the body. The onset of symptoms may be slow, the condition increasing over months or even years. Cough is the most common and persistent symptom. A glairy, mucoid material, tinged with blood or great quantities of oily liquid, which may contain hair, may be expectorated. In such cases the diagnosis is evident. Hemoptysis may be alarming and may even prove fatal. Difficult breathing is usually present. Pain, especially on exertion, is described as occurring over the tumor and radiating to the arm. The slow onset is helpful in differentiating the condition from pneumonia, empyema and pleurisy with effusion and other infectious processes. In most of the cases described, fever, loss of weight, loss of strength and anorexia are present.

Beye [1] says that with the typical clinical picture, it is not advisable to aspirate, but to proceed at once to perform thoracotomy. The symptoms typical of the condition, which make definite diagnosis possible, are of interest equally to the internist and to the surgeon, and I wish to express appreciation of Dr. A. H. Gunderson's untiring, painstaking efforts in the diagnosis of this, our first case of dermoid cyst of the mediastinum.

REPORT OF A CASE

History.—A. B., a woman, aged 22, single, a telephone operator, came to my office on June 19, 1926, complaining of pain in the chest and shortness of breath. Her family history was not important. Her father and mother were both living and well; no brothers or sisters had died. There was no history of tuberculosis, cancer or other chronic diseases in the family.

She had had the usual diseases of childhood, but no other illness except the present one. She associated it with an illness she had had five years before, when she had experienced a throbbing pain in the left elbow and shoulder, and a gripping pain in the left side of the chest, which she thought was pleurisy. These symptoms were more marked when she became weary, especially in the evening, and she had lost weight continuously for two months. She then developed an acute illness, which was diagnosed pneumonia, and which confined her to bed from July to December, 1921.

During the following summer she had had continually a sense of oppression in the chest, with coughing spells which lasted three or four days, and ended when she had coughed up a pint or more of grayish, foul-smelling fluid, occasionally tinged with blood. Her condition was diagnosed as pulmonary tuberculosis, and she was sent to Mexico for treatment. While there she gained in weight and felt better, although she frequently had attacks of pleurisy. The

next spring she again developed a sense of oppression in the chest, which lasted two or three days at a time, and which ended when she had coughed up about one pint of fluid. Her physician aspirated her chest and removed about a pint and a half of fluid; this procedure gave her marked relief. She improved rapidly and came to Everett about two years before she consulted me. She was fairly well until a year before, when she had again felt pressure in the chest and into the left shoulder and arm, and the cough and shortness of breath on exertion had returned. She did not have fever or chills. She lost some weight, and her symptoms gradually became more marked.

Physical Examination.—Examination revealed a young woman, slightly undernourished, 64 inches (162.6 cm.) tall and weighing 116 pounds (52.6 Kg.). She appeared a little restless and had a slight cough. There was slight prominence of the eyeballs, but no other phenomena of the eye suggestive of hyperthyroidism. The pupils were equal and reacted to light and in accommodation;

Fig. 1.—Roentgenogram showing the mediastinal tumor ten days before operation.

the sclera was clear. Examination of the ears, nose and throat showed that they were normal. The thyroid gland was not enlarged. The chest was slender and symmetrical, though there was slightly greater expansion on the right side than on the left. There was an area of dulness over the left side of the chest, extending from above the third rib downward over the cardiac area and from 2.5 cubic millimeters outside the left mammillary line to 5 cubic millimeters to the right of the sternum. Percussion showed that the right border of the heart was 5 cubic millimeters to the right of the midsternal line. The breath sounds over the left lung were free, with an occasional râle at the third interspace. The left border of the heart could not be outlined, as the area of precordial dulness merged with that of the tumor. The sounds of the heart were regular in both rate and rhythm and free from murmurs.

The gastro-intestinal organs were apparently normal, the abdomen did not show any evidence of tenderness, and no masses were present. Examination showed that the extremities were normal. The glands were not enlarged.

The urine was normal: examination of the blood showed hemoglobin, 85 per cent; erythrocytes, 4,300,000; leukocytes, 7,600; polymorphonuclear neutrophils, 61 per cent. The Wassermann reaction on the blood was negative.

Fluoroscopic examination revealed a large smooth mass in the mediastinum, the shadow of which measured about 10 cm. The heart was pushed markedly to the right, 8 centimeters to the right of the midsternal line. The excursion of the right lung was good. That of the left was limited because of pressure from the tumor. The mass was well anterior.

Exploratory Thoracocentesis.—The needle was inserted at the left fourth interspace, about 2 inches (5 cm.) from the sternum, with the patient under the fluoroscope. The needle, after being pushed through the wall of the chest, met firm resistance. It was carefully forced through the resisting area for about 1 inch (2.5 cm.). Then a mucoid, glycerin-like fluid began to leak away, and 450 cc. of it was removed. The patient did not experience any distress, and

Fig. 2.—Roentgenogram taken three months after the removal of the tumor shown in figure 1.

went to her home that evening. She was fairly comfortable for four weeks; then she returned, compaining of her old symptoms. The tumor was aspirated again, and 350 cc. of fluid was removed.

The chemical analysis of the aspirated contents from the dermoid cyst showed an oily, yellow, mucoid material containing crystals of cholesterin and some squamous cells. Microscopically, it showed fat droplets (cholesterin material) and a few squamous cells, but no hair.

Operation and Course.—On Aug. 29, 1926, the patient entered the General Hospital, and on August 30, 400 cc. of mahogany-brown fluid was removed; she again felt comfortable. On Sept. 1, 1926, an operation was performed under procaine hydrochloride and nitrous oxide anesthesia. An incision was made on the left side from a point on the lower border of the sternal end of the second costal cartilage, arching downward with a medial convexity to a point on the sixth rib, just below and outside the nipple. The breast and pectoral muscles were dissected completely from the wall of the chest, and the flap was turned

out. Three and a half inches (8.8 cm.) of the sternal ends of the third and fourth ribs were removed subperiosteally, and an incision was then made through the remaining wall of the chest (intercostal muscles, perichondrium, fascia) down to a point where dense fibrous tissue was encountered. I had expected to encounter the pleura in the exposure, but fortunately the cyst had forced the pleura of the left lung laterally to such an extent that the only connective tissue encountered by the incision was the wall of the dermoid cyst.

An aspirating needle was then passed through 1 inch (2.5 cm.)) of fibrous tissue before 400 cc. of fluid within the cyst could be aspirated. By careful sharp dissection and digital separation, a line of cleavage was found between the cyst and the left pleural sac. Separation along this line of cleavage was continued mainly by the right index finger; when digital separation became impossible, sharp dissection was continued until another line of cleavage, separable by the finger, was found. In this manner the entire cyst was freed and

Fig. 3.—Immense cavity in the mediastinum after removal of the cyst.

removed from the mediastinum. Five gauze packs were placed in the cavity left by the removal of the cyst. The entire thickness of the incised chest was approximated and held in position by three retention sutures of silkworm gut. The skin was approximated with skin clips.

Gross Pathologic Observations at Operation.—The cyst was 8½ inches (21.5 cm.) long and 4½ inches (11.3 cm.) at its greatest diameter, with a tapering apex. Its outer wall was composed of dense laminated, fibrous connective tissue, which was separated from the adjacent pleura and tissue of the mediastinum by a less dense and somewhat spongy layer of connective tissue. The average thickness of the wall of the cyst was one fourth of an inch (0.63 cm.). In two places it was thickened by the formation of papillomatous, teatlike projections about the size of a pea, which arose from the inner wall of the cyst by a broad base. The wall of the cyst on the side next to the lung was smooth and pearly, and was almost completely covered with a brownish, caseous or salve-like deposit, about one eighth of an inch (0.3 cm.) thick. The fluid within

the cyst was a dark mahogany brown. Since one point on the lining of the wall of the cyst appeared to have been the site of a recent hemorrhage, it seemed probable that the dark color of the fluid was due to a hemorrhage from this point. The cyst contained 400 cc. of fluid at the time of operation. Contrary to expectations, ectodermal derivatives, such as hair, teeth or nails, were not found in the cyst.

The patient's pulse became irregular and weak when traction was made on the cyst during its removal. One-half cubic centimeter of epinephrine was given subcutaneously, with good results. Her condition remained good otherwise throughout the operation.

Postoperative Course.—Postoperative recovery was uneventful. The patient rested quietly and required little morphine. On September 3, one gauze pack was removed. Two days later the other packs were removed, and considerable serosanguineous discharge was present. The wound was clean, and the patient's general condition was good, though she had some difficulty in breathing and required an occasional hypodermic of morphine to relieve pain.

Fig. 4.—Patient five days after the removal of the cyst.

On September 8, the patient's progress had been favorable. Because of elevation of temperature to 102 F., she was placed in the prone position, face downward, to secure better drainage, and, following a profuse discharge of serosanguineous material, her temperature declined to normal.

On September 10, the patient was up in a wheel chair. All sutures were removed, the wound was clean, and her general condition was good.

By September 18, she had been partly ambulatory for a week. She ate and slept well and breathed without difficulty. She admitted that her breathing was freer than it had been for months. The wound was clean, and, except for a granulating area 1 inch (2.5 cm.) in diameter, it was closing fast. She was discharged from the hospital with instructions to report at the office for further observation and for dressing.

On October 5, the office record showed that the wound had healed completely. The patient was feeling comfortable and well and gaining slightly in weight.

By Jan. 12, 1927, she had gained 15 pounds (6.8 Kg.) in weight. She had returned to work, and said she felt better than she had for five years. She did not have any discomfort in her chest. The operative wound was firmly healed, and to all appearances the result of the operation has been a complete cure.

Pathologic Report.—Sections made from the wall of the cyst showed epithelium, sebaceous glands and connective tissue.

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